Heated tobacco products: Potentials of harm reduction, improvement of indoor air quality and the need for further studies

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ABSTRACT

Air pollution is a major concern in the Philippines, with indoor and outdoor air pollution among the highest causes of mortality in the country. However, the latest regulations deal only with ambient outdoor air pollution. Indoor air pollution is seldom monitored or studied. Most of the official government monitoring data also deal with outdoor air pollution even if Filipinos spend more than 80% of their time indoors. Smoking indoors can be a cause of excess air pollutants in the indoor setting. Heated Tobacco products, newly introduced in the country, have been reported to reduce the harm of exposure to users to air pollutants. I investigated this through the review of 282 studies, research papers, books, and narratives about HTP use and their effects. These studies show reduced release of harmful and potentially harmful compounds (HPHC) in the aerosol and lower concentrations of HPHCs in the indoor environment when using HTPs as compared to tobacco smoke. Short term pre-clinical studies also show a reduction in the biomarkers for potential exposure to these HPHCs and risk calculations have shown a reduction in cancer potencies across populations. While long-term epidemiological studies are still required to determine with finality the risks that HTP use may have, there is already wide agreement in the initial results that the complete switch to HTP use from cigarette smoking presents less risks of harm. The review, however, shows that much has to be studied about the manner by which HTPs can affect indoor air quality in tropical countries such as the Philippines.

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INTRODUCTION

The right to breathe clean air is a basic right recognized under Philippine law as is the right to be informed of the right and extent of the potential hazard of any activity (Philippine Clean Air Act of 1999, Section 4, Recognition of Rights). Much of the information on air quality in the country is on outdoor air quality although the Philippine's Department of Environment and Natural Resources' last National Air Quality Report was issued for 2008-2015. Its Environmental Management Board has, however, issued yearly reports which show selected air quality reports for cities across the country (DENR-EMB 2021). Data for 2020 shows that national annual averages for Particulate Matter-10 microns (PM-10) are decreasing from 76 µg/NCM in 2011 to 27 µg/NCM in 2020. Particulate Matter-2.5 microns has also decreased from 20 µg/NCM in 2016 to 15 µg/NCM in 2020. These results were, however, affected by the lower economic and vehicular activities during the global COVID-19 pandemic, as was discussed in the report. International air quality organizations, such as IQAir, have consistently ranked Manila

KEYWORDS

heated tobacco products, indoor air quality, HTP, heat not burn

and the Philippines as having better air quality than many of its Asian neighbors, including Indonesia, Thailand, and Hong Kong (table from IQAIR.com), but this is due to the Philippines having the least number of monitoring stations per city in the region I (Madarang 2019). Despite favorable monitoring reports, the air quality in Metro Manila continues to be perceived as poor due to the persistently dire traffic conditions, which rank among the worst globally. Other Philippine major cities are also not immune to this, as majority of the air pollution in the country is attributable to mobile sources (about 81% of the pollution in Metro Manila is attributable to mobile sources according to DENR-EMB). The main advantages of the Philippines are the tropical climate, which allows for faster dispersion because of the elevated temperatures, the tropical cyclones which pass through the country, which wipes out most of the air pollution along its path, and the monsoon seasons, which remove particulate matter from the air during rainfall events. Hence, air quality annual averages tend to be lower, but air quality may spike during high traffic events in the summer months.

Even less information is found in literature for indoor air pollution and there are limited studies and standards for indoor air pollution in the country. Across the world, indoor air pollution has been recognized as a major source of exposure for both biological and chemical contaminants which may cause disease. In the United States, a study made in the 1990s showed that Americans spend 87% of their time indoors plus 6% in the confines of their car (Klepeis et al. 2001). In Metro Manila, a study conducted in 2016 shows that people spend 84% of their time indoors and 11% of their time commuting (Kecorius et al. 2018). While it was observed that this time commuting is almost twice that of the time spent commuting in the United States and about 2.2 times that in Europe, it should be emphasized that, based on this study, Filipinos spend about 20 hours of each day at work or at home in indoor settings. If the commute would involve airconditioned cars, buses, or trains, then Filipinos spend up to 22.6 hours per day in enclosed areas, and only 1.5-2 hours per day in the outside air environment.

Indoor air pollutants are a major source of exposure for many ailments and sicknesses. In fact, as part of the process of diagnosis of certain sicknesses, a doctor or a health care professional will ask about exposures in the house or workplace, including proximity to industries or to major roads, ventilation, the use of cooking materials, or a source of secondhand tobacco smoke. The awareness of smoking and its adverse effects are as widespread today as at any point of time in history (Seguel et al. 2016). Much of this has led to increased interest in smoking products that are reported to produce less harm due to less harmful constituents in its aerosols. Heated Tobacco Products (HTP) have been recently introduced in Philippine markets and are marketed as a reduced harm alternative to traditional smoking products. This paper aims to provide a summary of the major international studies on such products and their toxicological impacts as well as their impacts on indoor air quality and thus fulfill the requirement under the Philippine Clean Air Act to inform the population of the potential hazard of a particular activity.

OBJECTIVES

The main objectives of this paper are as follows.

- To scan documents and studies on heated tobacco products and provide summaries of the results of the effects of HTPs on indoor air quality and health
- To show how heated tobacco products affect indoor air quality in countries other than the Philippines
- To show the deficiency in indoor air pollution studies in the Philippines
- To make the case for further studies on the effects of HTPs on indoor air quality in the Philippines.

DATA PROCESSING METHODOLOGY

A total of 282 studies, articles, books, and other documents were downloaded and searched as part of this review. These studies were divided into General Indoor Air Documents, Philippine Indoor Air Documents, Indoor Air Documents involving Heated Tobacco Products, Risk Assessments, Toxicological Studies, and Scientific Reviews. Most of the included studies were taken from searches of PubMed and ScienceDirect databases and the search was undertaken until July 2021. Some data were also taken directly from websites providing data on air pollution, heated tobacco, and air pollution risks, as was required in the discussion.

DATA SYNTHESIS

All documents and articles were tabulated and their results summarized in order to determine the relevance to the objectives of the paper. Data were divided according to the method provided above although some overlaps were noted with regards to documents on toxicology and risk assessments. Since the paper focused on Heated Tobacco Products, majority of the papers reviewed and cited were those utilizing HTs.

The toxicological effects of HTP releases were tabulated and summarized together with the resultant effects of HTP on indoor air quality based on several studies in temperate countries. This was compared to indoor air quality standards in the Philippines and the resultant discussion is provided below.

DISCUSSION

Indoor Air Quality in General

Indoor environments represent a mix of outdoor pollutants prevalently associated with vehicular traffic and industrial activities, which can enter by infiltrations and/or through natural and mechanical ventilation systems, as well as indoor contaminants, which originate inside the building, from combustion sources (such as burning fuels, coal, and wood; tobacco products; and candles), emissions from building materials and furnishings, central heating and cooling systems, humidification devices, moisture processes, electronic equipment, products for household cleaning, pets, and the behavior of building occupants (i.e., painting, smoking, etc.) (Cincinelli and Martellini 2017). In developing countries, the major concern is the use of biomass fuels that may exacerbate cardio-pulmonary diseases especially among women and children (Fullerton et al. 2008). Provided below are some of the sources and effects of indoor air pollution.

- Fuel burning for cooking (either using fuel burning appliances or wood and charcoal)
- Smoking regular tobacco products
- Household cleaning materials using volatile organic solvents
- Outdoor air pollution from mobile or stationary sources that enters the enclosed area

Work on assessing the health effects of indoor pollution has been slower compared to outdoor air pollution due to a number of reasons, including:

- the fact that policy development in the air pollution field has focused on outdoor air pollution as a result of the correctly perceived need to deal with the high levels of outdoor air pollutants associated with both coal smoke and photochemical smog;
- the ready applicability of standards to outdoor concentrations of air pollutants;
- the feasibility of monitoring concentrations of outdoor air pollutants on a large scale;
- the focus of epidemiologists on defining coefficients linking outdoor concentrations of air pollutants with effects on health; and
- the fact that the science and policy communities have focused on the public health impacts of air pollution in wealthy developed countries, while often disregarding the larger burden of disease due to indoor air pollution from solid fuel burning in the developing world. (WHO, 2010)

Indoor Air Quality in the Philippines

Indoor Air Quality has not been a topic of vital importance in the Philippines, but the global pandemic has spurred some renewed interest in airborne contaminants in the household, albeit the interest is mostly in biological contaminants of concern. The Philippine Clean Air Act standards provide only three standards; one, for ambient air pollution, which is for pollutants mixed in the air in the general environment outdoors; two, for stationary sources, which are the emissions directly from the smokestack of pollution sources; and three, for mobile emission sources, primarily used in vehicular emission testing. Likewise, the Environmental Management Bureau of the Department of Environment and Natural Resources only provides monitoring data for outdoor air pollution in major cities across the country and only in very few locations. Recent data shows that the quality of air has improved due to limited vehicular activity in the country during the pandemic, but which may exceed standards once again when activity picks up when the pandemic fear eases.

The sole regulation for indoor airborne contaminants remains to be the Philippine Occupational Safety and Health Standards issued in 1989, which provides threshold limit values (TLV) for 445 chemicals listed in the regulation. TLVs refer to time weighted concentrations of these chemicals for an 8-hour workday and a total of forty-eight (48) hours work of exposure per week. Most of the TLVs listed in the regulations are shown in ppm (parts per million) and mg/m^3 (milligrams per cubic meter), which are 3 to 6 orders of magnitude higher than what is usually reported for aerosol studies of tobacco and heated tobacco products. Moreover, these standards may not be applicable for contaminants inside a normal Filipino household, in which the average Filipino would spend about 90 to 96 hours per week. Moreover, since these are workplace standards, these do not seem applicable to children who spend more time in the house.

There are also limited studies on Indoor Air Quality in the Philippine Setting. A survey done in 2011 found only 17 research studies on the field, of which 7 studies involved IAQ in local transportation systems (i.e., buses), 6 were on IAQ in educational institutions, and 4 were on IAQ in commercial buildings (Anastacio et al. 2011). Four subsequent studies were also found. One was on the IAQ pollutants of concern concentrations in different areas of an office building (Cordon et al. 2019). Another involved measurement of space temperature, space relative humidity and air velocity and determination of the concentration level of gaseous contaminants, biological contaminants, and particulate matter in an office building in Makati (Zali et al. 2015). The final 2 studies discussed the air pollutants inside hospitals in Metro Manila; one focused on particulate matter 2.5 (PM2.5) and associated elements (AEs), black carbon (BC), nitrogen dioxide (NO_2), sulfur dioxide (SO_2) and volatile organic compounds (VOCs) (Lomboy 2014) while the other sought to identify and apportion possible sources of indoor PM2.5 in an urban tertiary care hospital in the Philippines (Enoveso, et al. 2020).

The classification of Thysanoptera was adopted from the Thrips Wiki (2023), a widely accepted website. The genera and species under Panchaetothripinae were listed, and arranged alphabetically. The keys for the identification of 16 species in 12 genera were developed using morphology-based diagnostics of female thrips which is used worldwide. The taxonomic keys rely on superficial character states in guiding users toward thrips species identification, and photomicrographs of female, and male thrips when available were taken using Nikon Eclipse E200, and Olympus BX63 microscope. The principal structures used in characterizing a female thrips were illustrated, and shown in Figures 1 and 2.

Key takeaways from these Indoor Air Pollution Studies include the following:

- In the study involving the Office Building in Makati, the average values of the carbon dioxide concentration level obtained either approached closely or were beyond the American Society of Heating, Refrigerating and Air-Conditioning Engineers (ASHRAE) indoor air quality standards limit of 1000 ppm. On the other hand, based on the Philippines DOLE OSHC standard limit of 5000 ppm, the average values of the carbon dioxide concentration level were far below. Thus, the office space had good indoor air quality if DOLE-OSHC standard was used and poor indoor air quality if ASHRAE standard was used (Zali et al. 2015).
- In the investigation of an office building in Manila, for seasonal variations, CO_2, and Relative Humidity (RH) were noted to be higher during the wet season. On diurnal variations, CO2 and RH had an increasing trend as the day progressed in each area. Indoor and Outdoor CO_2 were also found to have some correlation (Cordon et al. 2019).
- In the study of hospital pollutants, it was found that much of the PM2.5 concentrations were from crustal (human skin) (Lomboy 2014) and outdoor sources and found that significant pollution from outdoor sources entered the premises (Enoveso et al. 2020).
- In a study of houses in the southern Philippines, it showed low 24-h average area concentrations of PM4 and CO: 72_g /m3 and 1 ppm, respectively. Personal exposure monitoring of CO, as a proxy for PM from biomass smoke, was also very low (1 ppm averaged over 24-h); however, peaks of acute exposure were evident during cooking times, typically ranging between 20 and 40 ppm, with peaks up to nearly 200 ppm. This was probably due to the proper ventilation of the kitchens of the households investigated (Saksena et al. 2007).

The case for Lower Risk Tobacco Products

Indoor Air Pollution is, in fact, along with Tobacco, one of the top causes of death in the world according to metrics compiled by the Institute for Health Metrics and Evaluation (IHME), an independent global health research center at the University of Washington in the United States. The global number of deaths per risk factor is presented as Figure 1. The situation in the Philippines is presented in Figure 2 with air pollution and tobacco still among the top five risks of death. In fact, respiratory disease and tuberculosis and cardio-vascular diseases have been the top two causes of death in the Philippines in the past 30 years (see Figure 3). As provided in Table 1, some of the major causes of pollution are combustion processes; be it industrial, vehicular, or even personal (tobacco) combustion. Eliminating one of these sources (tobacco combustion) is one of the main premises that is pushed for HTP as a lower risk alternative.

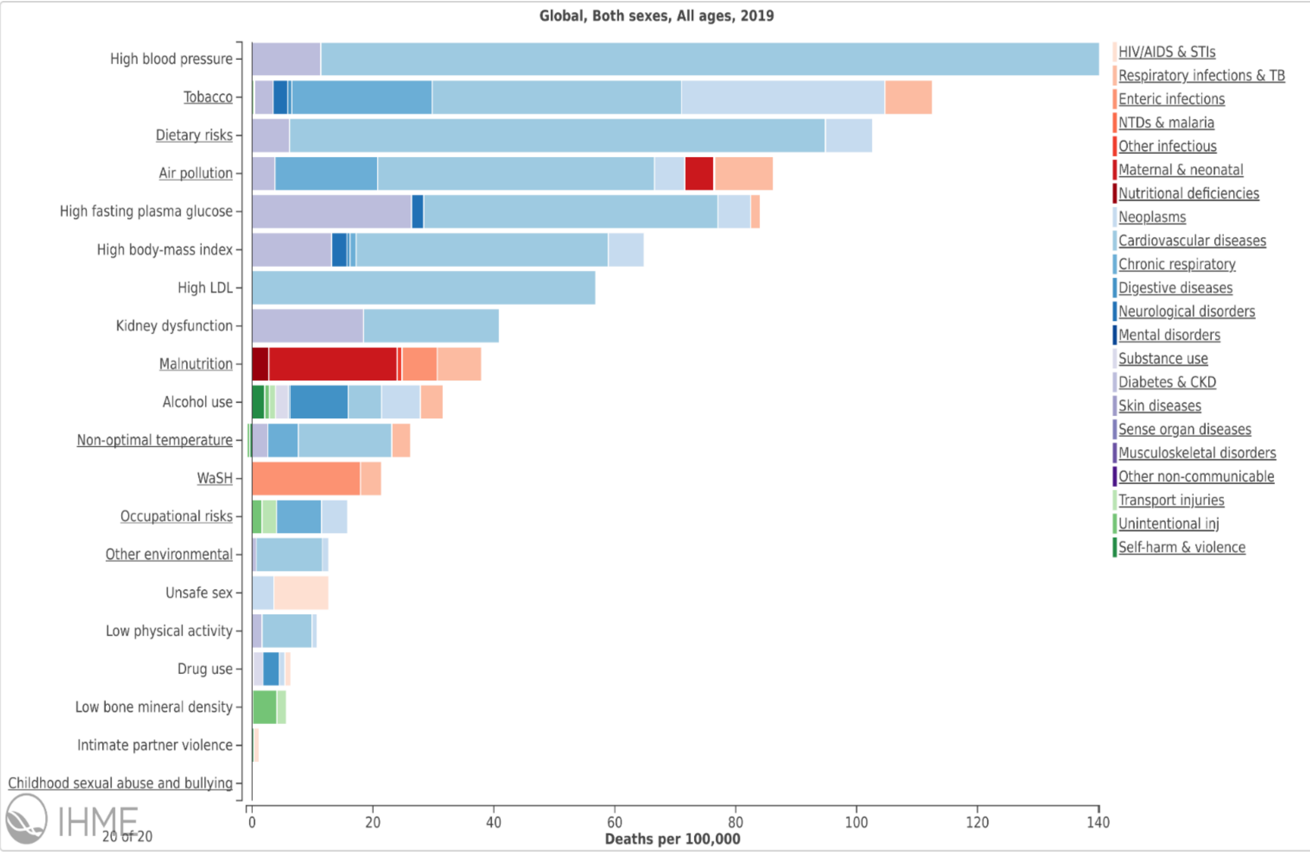

Figure 1: Global Total annual deaths by risk factor according to the Institute for Health Metrics and Evaluation (IHME)

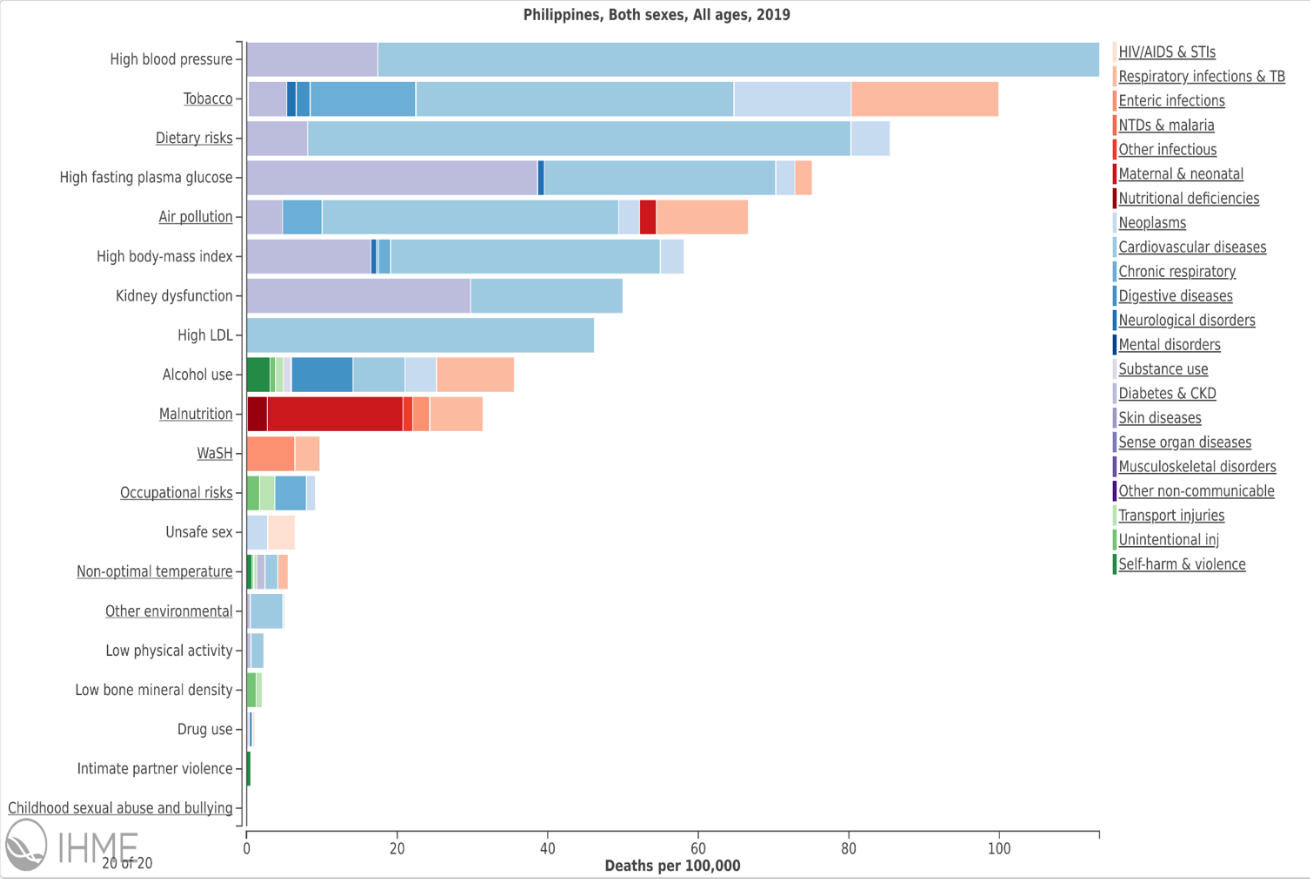

Figure 2: Philippine Total annual deaths per 100,000 population by risk factor according to the Institute for Health Metrics and Evaluation (IHME)

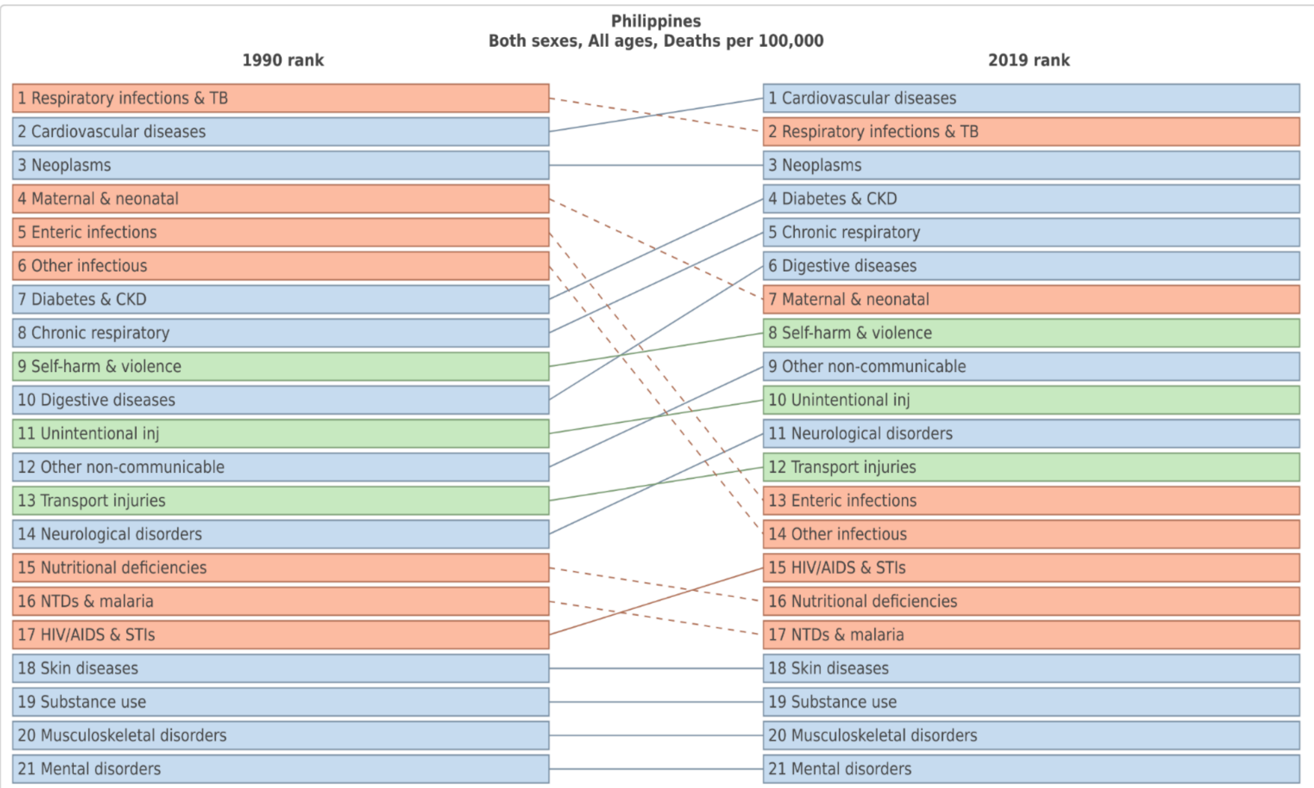

Figure 3: Top cause of death in the Philippines 1990-2019 (IHME)

Table 1: HnB products (Simonavicius et al. 2019)

HnB product and manufacturer	Release date, place	Description
Pax by Ploom (now PAX Labs)	2012, USA	Loose-leaf tobacco and cannabis vaporizer. loose tobacco is placed into a chamber and heated by an electrically powered element. A predecessor of Ploom Tech by JTI.
IQOS/THS 2.2 by PMI	2014, Japan, Italy, and Switzerland	IQOS includes a holder. a charger and tobacco sticks (Heets). A tobacco stick (about 320 mg) is inserted into the holder and the tobacco is heated with an electronically controlled heating blade which is inserted into tobacco plug. Operating heating temperature<350 °C. A single use lasts 6 min or up to 14 puffs. Under ISO conditions,12 puffs of the THS 2.2 yield 0.5 mg nicotine and 4.9 mg glycerol.
iFuse by BAT	2015, Romania	iFuse includes an electronic vapor device with a rechargeable Li-ion battery and an integrated circuit power controller, onto which a cartomizer (Neopod) is attached. The disposable neopod comprises an atomizer, a liquid tank with 1.15 ml of non-flavored nicotine liquid and a chamber containing a 130 mg tobacco plug. When the user presses a button, nicotine-containing vapor is produced, which is then drawn through the tobacco plug to absorb flavors. Before reaching the tobacco plug, the aerosol reaches an average maximum of <35°C.30
Glo/THP 1.0 by BAT	2016, Japan	Glo includes an electronic device with a rechargeable Li-ion battery and a heating chamber and tobacco sticks. A tobacco stick (about 260 mg) is heated in the heating chamber from the periphery. Operating heating temperature <250°C. Reaches operating temperature after 30-40s and a single use lasts for another 3 min.
Ploom Tech/PNT\ by JTI	2016, Japan	PNTV includes a power supply unit, a cartridge with a heater and liquid and a capsule with tobacco blend. Generates a nicotine-free vapor by heating the unflavored liquid; the vapor then passes through the tobacco capsule to absorb flavors and nicotine. Under HCI conditions,50 puffs yield 1.10 mg nicotine.
Carbon-heated tobacco product (CHTP) by PMI	Not released	A specifically designed electric lighter lights the carbon heating source which then heats a tobacco plug. Under ISO conditions,12 puffs of the CHTP yield 0.4 mg nicotine and 2 mg glycerol. 3 mg tar and 1mg *C0*. A predecessor of TEEPS by PMI.
IQOS/THS 2.1 by PMI	Not released	THS 2.1 includes a holder. a charger and tobacco sticks. A tobacco stick is inserted into the holder and the tobacco is heated with an electronically controlled heating blade. Operating heating temperature<400 °C. A single use lasts 6 min or up to 14 puffs. Under ISO conditions,12 puffs of the THS 2.1 yield 0.3 mg nicotine and 5 mg glycerol. A predecessor of commercially available IQOS/THS 2.2.

Extensive toxicological, experimental, and epidemiologic data, collected largely since the 1950s, have established that active cigarette smoking is a major preventable cause of morbidity and mortality (Spengler et al. 2001). In 1992, the US EPA completed a major assessment of the respiratory health risks of ETS (Respiratory Health Effects of Passive Smoking: Lung Cancer and Other Disorders EPA/600/6-90/006F). The report concludes that exposure to ETS is responsible for approximately 3,000 lung cancer deaths each year in nonsmoking adults and impairs the respiratory health of hundreds of thousands of children (USCPSC 2018).

Because of these assessments, the tobacco industry has tried to provide alternative products to regular cigarettes since the 1960s. Many of these initial products such as RJ Reynolds (now Reynolds America, part of British American Tobacco) Premier and Eclipse and Philip Morris' Accord and Heat Bar were marketed but received poor ratings from customers, were commercial failures and were withdrawn (Elias et al. 2018). The introduction of e-cigarettes in and around 2007 spurred renewed interest in providing alternative products and thus, paved the way for the introduction of heated tobacco products (HTP) in 2017-2018. In the Philippines, IQOS, a heat not burn product of Phillip Morris, has been available since 2019. In the subsequent parts of this discussion, I investigate the claims of reduced risk to both the user and the indoor environment of these new HTB products based on a review of literature and how the results from these studies may be applicable to the Philippines.

Heated Tobacco Products

Heated tobacco products (HTPs) are a form of nicotine delivery intended to provide an alternative to traditional cigarettes. These products were introduced for the first time in 1988, in the USA, as "Premier" from R.J. Reynolds. As in the case of electronic cigarettes, this technology initially did not gain wide popularity and was discontinued shortly after its introduction (Jankowski et al. 2019). In 2004, a product known as an e-cigarette were developed in China and were marketed as a less dangerous alternative to conventional cigarettes (Glantz 2018). This spurred the development of other alternatives. In 2014, a heated tobacco system from Philip Morris International (PMI), marketed as IQOS (I-Quit-Ordinary- Smoking), was introduced. Other tobacco companies introduced their own HTPs in 2016. British American Tobacco (BAT) created an HTP called "Glo", while a heated tobacco and e-cigarette hybrid was developed by Japan Tobacco (JT) and marketed as "Ploom TECH" (Jankowski et al. 2019). A more detailed list is provided in Error! Reference source not found. 1.

Iqos has three distinct components that perform different functions: (i) an Electrically Heated Tobacco Product (EHTP) - a multicomponent product containing a specially formulated tobacco substrate made from tobacco powder, water, glycerol, guar gum and cellulose fibers, (ii) a Holder into which the EHTP is inserted and that heats the tobacco portion of the EHTP by means of an electrically controlled heater, and (iii) a Charger that is used to recharge the battery in the Holder after each 360s heating cycle or when 14 puffs have been taken, whichever comes first (Cozzani et al. 2020).

The interest in these products lie in their claims of reduced harm owing to a difference in the type of aerosols that are produced from mere heating of the tobacco rather than burning. The mechanism by which HTPs create its distinctive aerosol was compiled from several studies by Cozanni (Cozanni et al 2020) and gives an indication of how different the processes are with HTPs. When samples of biomass such as tobacco are heated to temperatures above 100 °C, a number of thermal processes occur that result in the formation of three main product fractions: gases, liquid condensate and a residual solid. Upon heating, a tobacco sample first undergoes a drying process, usually in a temperature range between 100 and 300 °C. In this initial stage, dehydration of the tobacco takes place with the release of water and the evaporation of volatile organic compounds such as nicotine. Between 200–300 °C, torrefaction (mild-pyrolysis) processes result in the formation of low levels of low-molecular-weight gases (such as CO, CO_2 and NH_3), aldehydes, ketones, low-molecular weight hydrocarbons and aromatics and the tobacco substrate itself starts to change structurally. The liquid condensate generated at temperatures<300 °C is primarily generated from the evaporation of water and other volatile and semi-volatiles naturally present in tobacco (Cozzani, et al, 2020).

At higher temperatures, more complex processes take place. Pyrolysis is the thermochemical decomposition of biomass into a range of products, either with a limited supply, or in the total absence of oxidizing agents. High-temperature pyrolysis reactions result in the formation of a liquid condensate from the cooling and condensation of thermal degradation and depolymerization products from tobacco plant carbohydrates, fatty acids, waxes, phenolic compounds, lipids, alkaloids, proteins, peptides, amino acids, and organic salts. The residual solid that remains at temperatures>250 °C appears black in color and is both aliphatic and aromatic in nature. Heating to higher temperatures results in an increase in the aromaticity of the remaining solid with the evolution of light gases, aromatics, and polycyclic aromatic hydrocarbons (PAHs), as well as oxygen and nitrogen containing aromatics and PAHs (Cozzani, et al, 2020).

Harmful and Potentially Harmful Constituents

The systematic review of Simonavicius et al. in 2018 looked at 8 studies that provided levels of HPHCs in mainstream aerosols from HTB compared with cigarette smoke. Three more studies were added in this report and the table (Table 2) is provided below. The table provided compositions of HTP emissions comprising several substances based on smoking machines using either the International Organization for Standardization machine smoking regimen (ISO; 35 mL puff volume, 2 s puff duration, 30 s intervals between puffs, 14 puffs) or the Health Canada Intense regimen (HCI; 55 mL puff volume, 2 s puff duration, 30 s intervals between puffs, 14 puffs). The HCI regimen yields higher levels of harmful and potentially harmful compounds (HPHC), but no machine smoking regimen corresponds to human smoking and exposure, and their relevance to HTP use is not tested either. Reference products also differed between studies: the majority used 3R4F tobacco cigarettes (a reference product developed for research), others used commercially available cigarettes and e-cigarettes (cigar-like, pen-style and tank-style) (Simonavicius et al. 2018). Regular HTP blends had R. before their brand name while the M. stood for the menthol variety.

Table 2: HPHC and other components in HTB aerosols as compared to reference cigarettes.

	Schaller *et al.* 2016 (Part 2)	Schaller et *al.* 2016 (Part 3)		Jaccard *et* al. 2017	Auer *et* al. 2017	Bekki *et* al. 2017		Eaton *et* al. 2018	Forster *et* al. 2018			Poynton *et* al. 2017	Mallock et al. 2018	Salman et al. 2019	Cozzani 2019
Affiliation	PMI	PMI		PMI	University of Bern, Switzerland	National Institute of Public Health, Japan		BAT	BAT			BAT	German Federal Institute for Risk Assessment	National Institute on Drug Abuse of the National Institutes of Health and the Center for Tobacco Products of the US Food and Drug Administration	PMI
Tobacco stick	R. IQOS	R. IQOS	M. IQOS	R. IQOS	R. IQOS	R. IQOS	M.IQOS	R. GLO	R. IQOS	R. Glo	M. Glo	R. iFuse	IQOS	IQOS	IQOS
Reference cigarette	3R4F	3R4F	3R4F	3R4F	Lucky Strike Blue	3R4F	3R4F	3R4F	3R4F	3R4F	3R4F	3R4F	different combustible cigarettes, including low and	Marlboro Red	3R4F

	Schaller *et al.* 2016 (Part 2)	Schaller et *al.* 2016 (Part 3)		Jaccard *et* al. 2017	Auer *et* al. 2017	Bekki *et* al. 2017		Eaton *et* al. 2018	Forster *et* al. 2018			Poynton *et* al. 2017	Mallock et al. 2018	Salman et al. 2019		Cozzani 2019
													high tar, slim, and reference cigarettes			
Puffing regimen	HCI	HCI	HCI	HCI	ISO	HCI	HCI	HCI	HCI	HCI	HCI	HCI	HCI	ISO	HCI	HCI
1,3-Butadiene	<1%	<1%	<1%	<1%	-	-	-	<1%	<1%	<1%	<1%	<1%	0.2%--0.3%			0.305%
1-Aminonaphthalene	<1%	<1%	<1%	<1%	-	-	-	-	<1%	<1%	<1%	<1%				0.313%
2-Aminonaphthalene	<1%	<1%	<1%	<1%	-	-	-	-	<1%	<1%	<1%	3%				0.284%
3-Aminobiphenyl																0.516%
4-Aminobiphenyl	<1%	<2%	<2%	<1%	-	-	-	-	<1%	<1%	<1%	3%				0.516%
Acetaldehyde	12%	14%	13%	13%	22%	-	-	5%	15%	5%	5%	<1%	12.8%-19.5%		28.466%	13.315%
Acetone															6.236%	4.725%
Acrolein	7%	7%	6%	6%	82%	-	-	1%	6%	1%	2%	5%	6.1%-10.5%			5.895%
Acrylonitrile	1%	<1%	<1%	<1%	-	-	-	-	<1%	<1%	<1%	<1%				0.766%
Ammonia	38%	36%	35%	36%	-	-	-	-	33%	12%	15%	<50%				
Benzene	<1%	<1%	<1%	<1%	-	-	-	<1%	<1%	<1%	<1%	<1%	0.6%-1.2%			0.606%
Benzo[a]pyrene	7%	9%	8%	6%	8%	-	-	<3%	5%	2%	3%	<7%				3.497%
Butyraldehyde															138.486%	25.055%
Catechol																17.221%
Carbon monoxide	1%	2%	2%	1%	-	1%	1%	<1%	1%	<1%	<1%	21%				1.617%
Crotonaldehyde	<6%	6%	5%	<6%	4%	-	-		5%	1%	2%	<3%	4.2-9.1%		13.657%	3.963%
Formaldehyde	11%	10%	8%	9%	74%	-	-	6%	11%	6%	7%	13%	3.8%-17.1%		26.814%	8.736%
Glycerin																190.652%
Hydroquinone																7.784%
isoprene	<1%	<1%	<1%	<1%	-	-	-	-	<1%	<1%	<1%	<1%	0.2%-0.4%			0.268%
m-Cresol																0.938%
Methyl Ethyl Ketone																3.706%
Methacrolein															7.641%	

	Schaller *et al.* 2016 (Part 2)	Schaller et *al.* 2016 (Part 3)		Jaccard *et* al. 2017	Auer *et* al. 2017	Bekki *et* al. 2017		Eaton *et* al. 2018	Forster *et* al. 2018			Poynton *et* al. 2017	Mallock et al. 2018	Salman et al. 2019		Cozzani 2019
NO																3.658%
NOx (NO + NO2)																3.468%
o-Cresol																1.667%
p-Cresol																0.860%
Phenol																10.547%
Propionaldehyde															46.461%	11.440%
Pyridine																21.652%
Quinoline																1.429%
Resorcinol																1.775%
NNN	5%	6%	4%	4%	-	6%	8%	9%	4%	9%	7%	<1%				
NNK	3%	3%	2%	3%	-	5%	5%	2%	4%	2%	2%	<1%				
Styrene													1.4%-3.1%			4.121%
Toluene	2%	1%	1%	1%	-	-	-	-	1%	<1%	<1%	2%	1.2%-2.4%			1.234%
Nicotine	73%	70%	64%	61%	84%	65%	71%	-	57%	23%	18%	139%	40%-100%	96.250%	83.333%	68.750%
Water	203%	231%	188%	-	-	328%	350%	-	168%	80%	71%	-	up to 322%			220.859%
Glycerol	203%	191%	163%	-	-	-	-	-	182%	129%	101%	-				
Total particulate matter	122%	98%	89%	-	-	119%	135%	-	104%	56%	54%	-	84%-191%	128.913%	72.453%	119.214%
Tar/nicotine-free dry particulate matter	79%	33%	40%	-	-	39%	53%	-	75%	46%	48%	-	52%-132%			62.319%

Note: R. Iqos means regular IQOs while M. Iqos refers to menthol

All studies showed reductions in HPHCs except for Butyraldehyde, which yielded higher levels using the HCI regimen in the study of Salman, and total particulate matter in at least 6 of the 11 studies provided. The Butyraldehyde increase may be due to the smoking regimen used (as stated, HCI may release greater amounts of aerosol substances), although Salman found that the total amount of carbonyls released by HTPs as compared to a reference cigarette were reduced in his study. The study of Mallock, et al, surmised that since aerosols of HTPs contain a comparatively high proportion of water, standard analytical procedures cannot be easily applied since water is trapped on the glass fiber filter used and therefore accounts for the total particulate matter (TPM) (Mallock et al 2019). Furthermore, the Protano study concluded that the levels of submicroscopic particulates released by cigarettes are four times that of electronic and HTP use and that the levels of these submicroscopic particulates return to normal background concentrations almost immediately in the case of HTP and e-cigarettes (Protano et al. 2020). The study presumed that submicroscopic particles coalesce with each other rapidly and settle in large numbers. It also suggested that the high level of particulate matter may be due to the side stream emissions of HTP devices. Finally, two studies made by Karkela, et. Al (2021) and Pratte, et al. (2017) showed that no solid particles were detected in Iqos products indicating a lack of combustion in the process of producing the aerosols in the device. Since these studies focused primarily on particulate matter, these were not included in **Error! Reference source not found.**.

In all studies, higher levels of water and glycerol were also found which is consistent with the volatilization mechanism of HTPs. As concluded by Cozzani et al. (2020) in his investigation on the operation of a heated tobacco product, “in contrast to the smoke aerosol formed from the combustion and high temperature pyrolysis of tobacco in a cigarette, the EHTP aerosol is generated by the condensation of vaporized compounds originally present in the tobacco substrate, principally glycerol, water, and nicotine.” In fact, a comprehensive study of the constituents of the HTP aerosols found a total of 529 chemical constituents, excluding water, glycerin, and nicotine, were present in the mainstream aerosol of IQOS, generated by following the Health Canada intense smoking regimen, at concentrations ≥ 100 ng/item (Bentley et al. 2020). 402 of these chemical constituents are present in particulate matter of the aerosol while 39 were present in both the particulate matter and vapor. It was found however, that only a small number of compounds, apart from water and glycerin, exceeded the amount found in the reference cigarette. These included the following with descriptions taken from PubChem, the chemistry database of the National Institute of Health of the US (https://pubchemdocs.ncbi.nlm.nih.gov/):

- 1-Hydroxy-2-propanone/1,2-propenediol, a flavoring additive
- Propylene glycol, a synthetic liquid chemical, food, and pharmaceutical additive
- Pyranone
- Furfural, a flavoring agent, or adjuvant and is not toxic at levels below 0.5 mg/kg body weight.
- 2-Monoacetin
- 2-Furanmethanol, a food flavoring
- 3-Chloro-1,2-propanediol, Used as a chemical intermediate for the synthesis of diprophylline; glycerol alpha-allyl ether; guaifenesin; iohexol.
- 3-Methylpentanoic acid, a flavoring agent
- 1-Acetyloxy-2-propanone, a flavoring agent and cleaning agent
- Heptacosane, a volatile oil component and a plant metabolite.

In order to show the differences more clearly in the aerosol content of the two (HTP and Cigarettes), the illustration provided as Figure 4 was provided by Hirn, et. al. in 2020. More than 70 % of the HTP aerosol particulate matter consisted of propylene glycol (PG) and vegetable glycerol (VG), whereas the 3R4F reference cigarette smoke consisted primarily of "others". Taken together, the data on the composition of the aerosols provides compelling evidence of the following:

- HTP, such as Iqos, produces aerosols without combustion from its heating sticks that have almost the same number of compounds as the aerosol of a reference cigarette but of a vastly different composition.
- Majority of harmful or potentially harmful compounds are reduced by one or two orders of magnitude in the aerosols of HTP.
- However, the high levels of total particulate matter, is a concern. It should be investigated if this is due to the interference of water only. Even more important is to determine the effects of the submicroscopic particles produced in the aerosol.

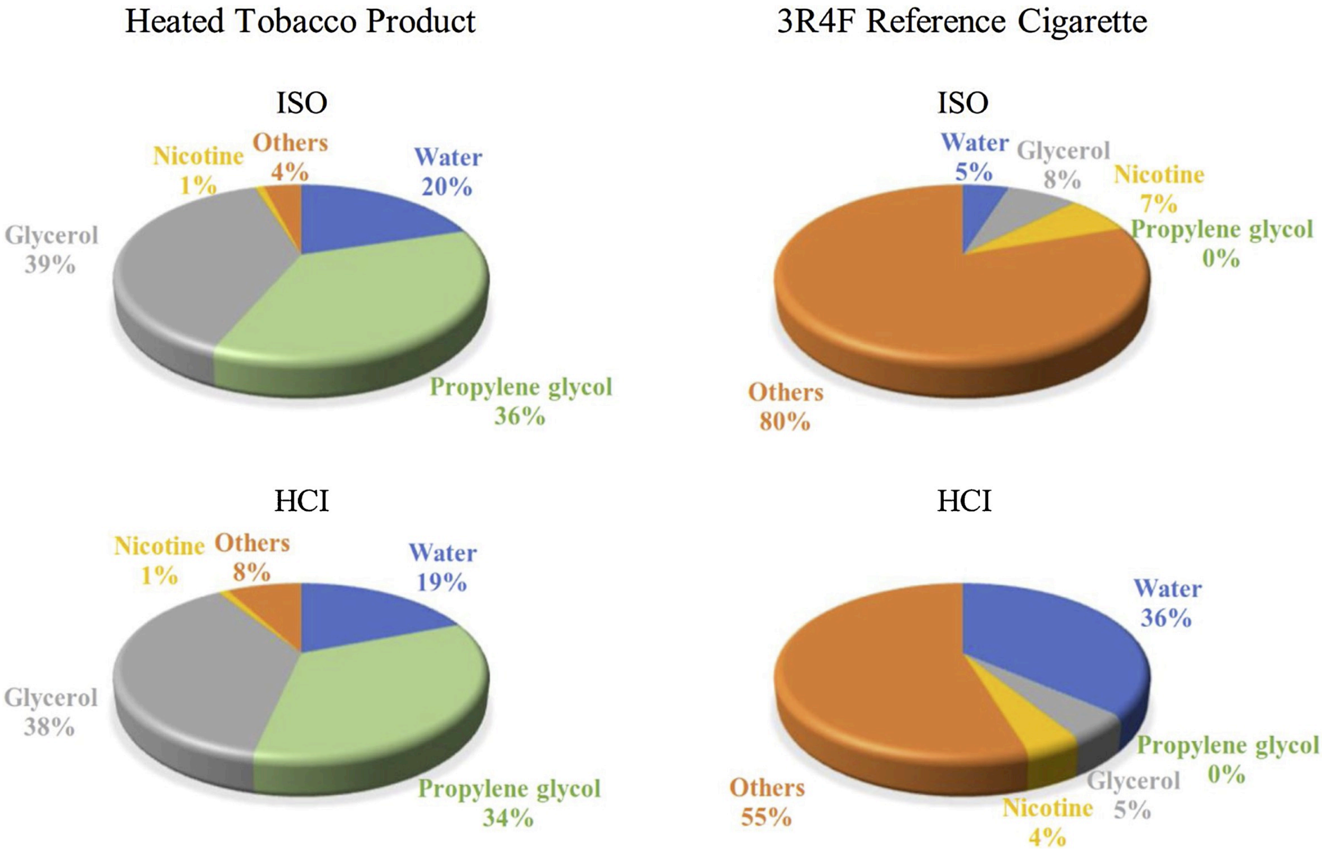

Figure 4: Major Constituents in the HTP Aerosol (left panel) and the 3R4F Reference Cigarette Smoke (right panel) collected onto the Cambridge filter pads under the ISO (upper panel) or the HCI (lower panel) smoking regimes.

HTP Aerosols impact on indoor air quality

As opposed to measuring the concentrations of the aerosol itself, several studies were also conducted to determine what were the effects of HTP use on indoor air quality. Simonavicius et al. (2018) provided a summary of the results of studies of changes in indoor air quality as a result of the use of HTP products as compared with reference cigarettes. Three studies were included in the original table; three subsequent studies were included while a fourth, a 2008 study was also added. The resulting table is presented in Table 3. Across the board, we see reductions in the level of pollutants in indoor air quality when HTP is used as compared to cigarettes. Important carcinogens, such as aldehydes and volatile organic compounds, were found to be reduced by about 75 to over 99%. The lowest reduction was for formaldehyde which reduced from 78 to 93% Toxicants like tobacco-specific N-nitrosamines (TSNAs), formed primarily during curing and processing of tobacco rather than by combustion, were also present in the filler of HTP consumables. However, compared to cigarette mainstream smoke TSNA levels were reduced by about 90-99% in the indoor air concentrations.

Table 3: Relative levels of HPHC and particulate matter in indoor air from HnB products

	Ruprecht *et al.* 2017	**Mitova *et al,* 2016**	**Forster *et al.* 2018**	**Hirano et al. 2020**						**Tricker et al, 2008**			**Savdie et al. 2020**		**Protano at al. 2020**	
Affiliation	National Cancer Institute, Milan, Italy	PMI	BAT	Ministry of Health, Labor, and Welfare under the Fund for Tobacco Research and Analysis Project, Government of Japan						PMI			LIFE Index-Air project		Sapienza University of Rome, Rome, Italy;	
HnB	IQOS	IQOS	Glo	Ploomtech	Ploomtech	GLO	GLO	IQOS	IQOS	IQOS			IQOS		IQOS	
Reference cigarette	Conventional cigarette	Marlboro Gold	Lucky Strike Regular	Melvius 1	Melvius 1	Melvius 1	Melvius 1	Melvius 1	Melvius 1	Marlboro			Chesterfield		Marlboro Gold	
Setting	'A sitting room' (ACH=1.5)	'Residential' (ACH=1.2)	'Home' (ACH=1.2)	Shower Cubicle (ACH=0)	Office (ACH=0)	Shower Cubicle (ACH=0)	Office (ACH=0)	Shower Cubicle (ACH=0)	Office (ACH=0)	High IAQ office (ACH = 4.9)	Medium IAQ office (ACH =3.1-3.3)	Low IAQ office (ACH = 1.6 to 1.8)	73 sqm house in Portugal	(Diesel Opel Corsa	fully enclosed 52.7 cubic meter room	
Secondhand emissions' markers															AVERAGE	HIGHEST
370 nm UV BC (µg/ m3)	0.7%-0.8%	-	-													
PM>0.3 (particles/ cm3)	2.8%-7.3%	-	-													
PM$_{nm}$ (particles/cm3)	22.0%-24.0%	-	-										32.455%	13.5784%		
PM 1 (µg/m3)	0.9%-1.0%	-	HnB < background										2.323 %	0.9897 %	4.54%	17.49 %
PM 2.5 (µg/m3)	1.3%-1.5%	Non-detectable	HnB < background	0.1724 % to 0.1963 %	1.61% to 1.72%	1.7069 % to 3.0841 %	12.90 % to 26.98 %	4.59% to 7.12%	1.59 % to 1.85 %				2.345 %	0.989 %		
PM 10 (µg/m3)	1.5%-1.7%	-	HnB < background										2.523 %	0.9448 %		
Ultraviolet particulate matter	-	Non-detectable	-							7.52%	7.172%	9.720%				
Fluorescent particulate matter	-	Non-detectable	-							4.00%	3.103%	5.893%				
Solanesol	-	Non-detectable	-							13.23%	15.152 %	13.302 %				
3-Ethenylpyridine	-	Non-detectable	Non-detectable							5.46%	2.920%	2.128%				
HPHC																
1,3-Butadiene	-	Non-detectable	Non-detectable							0.88%	0.749%	0.396%				
Acetaldehyde (µg/ m3)	5.0%-5.9%	6.0%	2.2%							2.70%	10.000 %	9.084%				
Acrolein (µg/m3)	1.8%-2.3%	Non-detectable	Non-detectable							negative (decreased in iqos room)	10.390 %	3.457%				

	Ruprecht *et at.* 2017	Mitova *et al,* 2016	Forster *et* al. 2018	**Hirano et al. 2020**						**Tricker et al, 2008**			**Savdie et al. 2020**		**Protano at al. 2020**	
Acrylonitrile	-	Non-detectable	Non-detectable													
Benzene	-	1.7%	HnB = background							negative (decreased in iqos room)	negative (decreased in iqos room)	negative (decreased in iqos room)				
Carbon monoxide	-	3.8%	Non-detectable							negative (decreased in iqos room)	11.905%	66.667%	31.010%	11.0899%		
Crotonaldehyde	-	Non-detectable	Non-detectable							0%	0%	0%				
Formaldehyde (µg/ m3)	6.9%-7.1%	7.6%	10.2%							negative (decreased in iqos room)	22.621%	0.000%				
Isoprene	-	HnB < background	HnB < background													
Toluene	-	HnB < background	3.7%							negative (decreased in iqos room)	289.922%	negative (decreased in iqos room)				
Nicotine	-	6.2%	HnB < background	1.07% to 2.81%	0.26% to 0.37%	4.58% to 15.3846%	1.77% to 1.88%	8.76% to 24.7115%	1.6875% to 2%	0.40%	3.475%	2.392%				
Nitrogen oxides	-	HnB < background	HnB < background							8.33%	22.222%	25.000%				
Nitrogen oxide	-	HnB < background	HnB < background							negative (decreased in iqos room)	33.333%	138.095%				
Others not included in the original tables																
2-aminonaphthalene (ng/m3)										negative (decreased in iqos room)	negative (decreased in iqos room)	7.317%				
4-aminobiphenyl(ng/M3)										4.29%	1.852%	0.000%				
benzo[a]pyrene (ng/m3)										negative (decreased in iqos room)	22.556%	10.000%				

	Ruprecht *et at.* 2017	Mitova *et al,* 2016	Forster *et* al. 2018	Hirano et al. 2020						Tricker et al, 2008			Savdie et al. 2020		Protano at al. 2020	
Ethylbenzene (µg/m3)										negative (decreased in iqos room)	9.124%	negative (decreased in iqos room)				
m-/p-Xylene (µg/m3)										negative (decreased in iqos room)	11.636%	negative (decreased in iqos room)				
NNK (ng/m3) a										5.82%	0.000%	1.689%				
NNN (ng/m3) a										0.00%	0.000%	0.000%				
o-Toluidine (ng/m3)										negative (decreased in iqos room)	1.633%	7.143%				
o-Xylene (µg/m3)										negative (decreased in iqos room)	19.807%	negative (decreased in iqos room)				
phenanthrene(ng/m3)										negative (decreased in iqos room)	19.675%	1.923%				
propionaldehyde (µg/m3)										5.39%	14.343%	11.306%				
pyrene (ng/m3)										negative (decreased in iqos room)	139.151%	21.244%				

One test by Hirano et. al, (2020) in a totally enclosed unventilated shower room, found very high levels of Nicotine and PM2.5 after 50 puffs but these were reduced to below tolerable levels (in Japan) for PM2.5 and nicotine when done in an unventilated, 25 cubic meter room. When compared to cigarette smoke, however, these values were from 80 to 99% lower. As provided above, there were also studies that found particulate matter concentrations return to background levels almost immediately after smoking HTP. Only Tricker et al. (2009) saw an increase in toluene concentration, but this may be an outlier since in the low and high IAQ rooms, toluene concentrations actually decreased after HTP use when compared to the background concentrations. Of interest is the test conducted within a car made by Savdie et al. in 2020, which showed from 86 to 99% reduction in selected particulate matter fractions and 88% reduction in carbon monoxide when HTP were used in an enclosed car when compared with smoking a reference cigarette.

What is not included in these indoor air studies are propylene glycol and glycerol, which have the highest concentrations in the aerosols, according to the previous section. While propylene glycol and glycerol are approved as food additives and are safe for oral use, no long-term studies exist on potential health effects from human inhalation. Employees in the entertainment industry, who are regularly exposed to propylene glycol-containing aerosols such as theatrical mist, suffer more often from respiratory irritations and restricted lung function than unexposed persons (Varughese et al. 2005).

Comparing the recorded concentrations in indoor air with that of Philippine Occupational Safety and Health standards of the Philippines (1989) may not be helpful since the standards are outdated and are provided in mg/m^3 as compared to the µg/m^3 and ng/m^3 reported in the studies. Nonetheless, a comparison of the OSH standards and actual values reported by Tricker are presented in Table 4. As can be gleaned in the table, the OSH standards are way above the indoor air quality results of the said study. Note that these OSH standards were made in 1989, more than 30 years ago, and should be updated. Moreover. these are specifically meant to protect workers from emissions produced in the workplace and should not be used as a measure of the relative harm that these substances may have in residential areas, considering that people spend more time in their residences than in the workplace on the average.

Table 4: Results of Tricker et al. 2008 as compared to OSHA standards.

	High		Medium		Low		OSHA
	EHCSS (Simulation 1)	CC (Simulation 5)	EHCSS (Simulation 1)	CC (Simulation 5)	EHCSS (Simulation 1)	CC (Simulation 5)	
Number of smokers	2	2	2	2	2	2	
Number of cigarettes	10	10	10	10	10	10	
Air changes/h	4.90	4.90	3.10	3.30	1.60	1.80	
Online measurements							
CO (ppm)	0.10	0.83	MO	1.	0.27	1.58	50
CO2 (%) b	0.09	0.11	0.11	0.13	0.12	0.15	5000
NO (ppb)	27.00	22.00	40	78	23.00	48.00	25000
NO2(Ppb)c	25.00	39.00	19	49	14.00	36.00	5000
Particles, online (µg/m3)	28.00	200.00	64	346	110.00	586.00	
Offline Measurements							
1,3-Butadiene (µg/m3)	0.58	3.91	0.83	6.	0.94	10.10	2,200,000
2-aminonaphthalene (ng/m3)	0.18	0.42	0.184	0.593	0.28	1.05	
3-ethenylpyridine (3-vinylpyridine) (µg/m3)	0.09	1.11	0.141	1.40	0.16	2.02	
4-aminobiphenyl(ng/M3)	0.02	0.09	0.024	0.127	0.02	0.20	
Acetaldehyde (µg/m3)	2.36	11.40	4.	17.	5.25	28.00	360,000
Acrolein (µg/m3)	0.23	1.24	0.44	2.	0.51	3.99	250
Benzene (µg/m3)	2.08	3.32	3.	5.	1.75	7.44	80000
benzo[a]pyrene (ng/m3)	0.04	0.10	0.068	0.211	0.02	0.31	
crotonaldehyde (µg/m3)	0.15	0.40	0.15	0.33	0.15	1.10	6000
Ethylbenzene (µg/m3)	1.12	1.05	1.	4.	0.85	2.45	435000
Florescent PM-scopoletin (µg/m3)	0.09	1.82	0.124	3.	0.35	5.48	

	High		Medium		Low		OSHA
	EHCSS (Simulation 1)	CC (Simulation 5)	EHCSS (Simulation 1)	CC (Simulation 5)	EHCSS (Simulation 1)	CC (Simulation 5)	
Formaldehyde (µg/m3)	8.47	10.50	11.	14.	12.60	18.40	6000
m-/p-Xylene (µg/m3)	4.45	3.53	5.20	13.	3.18	7.79	43500
Nicotine (µg/m3)	0.08	5.00	0.212	5.30	0.27	6.94	500
NNK (ng/m3) a	1.15	4.01	0.30	4.	0.69	5.63	
NNN (ng/m3) a	0.25	0.79	0.25	1.	0.25	0.72	
o-Toluidine (ng/m3)	6.32	11.30	7.	16.	7.96	18.07	22000
o-Xylene (µg/m3)	1.45	0.95	2.	3.	1.03	1.97	435000
Particles, grav. (µg/m3)	24.50	84.50	41.	130	54.80	228.00	
phenanthrene (ng/m3)	10.88	9.38	11.	21.	10.60	21.40	
propionaldehyde (µg/m3)	0.55	2.32	0.79	3.	1.19	5.68	
pyrene (ng/m3)	2.32	3.19	4.	4.	1.59	3.79	
Solanesol (µg/m3)	0.30	1.94	0.696	4.	1.19	8.62	
Toluene (µg/m3)	9.17	8.83	13.	14.	10.83	39.18	375000
Ultra Violet PM-THBP (µg/m3)	0.82	9.35	1.	15.	2.89	29.10	

HTP Risk

Considering both the aerosol content and the indoor air quality are much reduced when using HTP as compared to cigarettes, there appears to a case to state that there is a lower risk of harm when comparing IQOS or HTP use and cigarette smoking. However, developing complete epidemiological studies and risk assessments will need many more years of data; epidemiological studies typically take 20 to 40 years to complete. There are, however, many studies that have calculated reductions in cancer potencies (Rodrigo et al. 2021) or reduction in attributable deaths to switching to HTP (Lee et al. 2018) or e-cigarettes (Levy et al. 2018). Even Phillip Morris has developed a Population health Impact Model to quantify, in the absence of epidemiological data, the effects of marketing a candidate modified risk tobacco product (cMRTP) on the public health of a whole population (Djurdjevic et al. 2018). All calculations estimate a reduction in possible deaths and incidence of cancer because of switching to HTP. Several studies on the short-term effects of HTP vs Cigarette smoking on biomarkers to HPHCs. One 90-day study found biomarkers of exposure to HPHC to be 40-95% lower after 5 days and reductions were sustained (36% to 93%) up to day 90 (Bosilkovska et al. 2020). Another 3-month study showed that even biomarkers of potential harm were reduced (Haziza et al. 2020). The significant reduction (>99%) of key carcinogens according to Fowles and Dybing (2003), such as benzene and 1,3-butandien, as well as the substantial overall reduction of toxicants is expected to affect health risks if people abstain completely from other tobacco products. In a detailed modeling assessment, Stephens (2018) compared relative harmfulness of different nicotine products with a model based on exposure data and cancer potencies. The calculated lifetime cancer risk of the HTP, using one data set by the manufacturer, was one to two orders of magnitude lower compared to combustible cigarettes but higher compared to e-cigarettes. Lachenmeier et al. (2018) calculated the combined margin of exposure (MOE) for the HTP and for combustible cigarettes. The obtained ratio between exposure and toxicity effect levels, which could be interpreted as a "safety buffer," was 10-fold higher for the HTP as compared to combustible cigarettes (Mallock, et al, 2019).

Care must be taken, however, in construing HTPs as totally risk-free products. The harmful and potentially harmful constituents present in cigarettes are still present in HTP albeit in much reduced quantities. This mixture of constituents has not been shown to reduce long term risk of exposure simply because they have not been enough time to do so. The studies provided in literature are all short term 5 day to 90-day trials which may be indicative of a short-term trend in reduction of harm. But the considerable risk of deaths due to tobacco products as provided in the foregoing discussions means that we do not the luxury of time to wait for further and longer epidemiological studies to confirm the current observation that these HTP does reduce the harm of use of tobacco products. Based on the plethora of evidence already compiled, the reduction in harmful components is expected to have a positive effect on the health risks of tobacco.

Impact on the Philippines

Philippine air pollution is dominated by mobile sources, with about 70% of the air pollution coming from vehicles and other line sources. Within cities and urban areas in the country, indoor and outdoor air pollution may mimic the pollutants from vehicular emissions while in rural communities, pollution from cooking using biomass may exacerbate indoor air quality during specific times. The contribution of tobacco smoke to indoor air quality has not been estimated so the level of reduction that HTP use may bring is not yet established the lack of indoor air quality awareness is also prevalent, even if air pollution is a top risk for morbidity and mortality, and, in particular, COPD. Moreover, smoking is banned in indoor public areas and some cities have even banned smoking outside outright (such as Iloilo). If the results of the international studies on the harm reduction potential of HTP can be made, then the shift from cigarette to HTP use should be a part of a concerted program to reduce the risk of respiratory diseases for people who could not quit smoking altogether.

Future Research

More definitive studies on the epidemiological risks of HTPs will need more time as the product will have to go to clinical studies and population or sub-population wide epidemiological data which can last for decades.

Most of the data regarding indoor air pollution has been from temperate climates with lower humidity which may not be applicable to the Philippines due to the differences in dispersion patterns of air pollutants This dispersion is dependent on the atmospheric conditions which will be different for tropical countries. The design of houses and buildings will also be important in determining where the Thus, there is a need for new original research on the effects of cigarette and HTP use on indoor air quality in the Philippines. The difference between the measured values of indoor air quality when either HTP or cigarette is used can then be compared with indoor air quality standards in the Philippines.

Likewise, research on the concentrations of propylene glycol and glycerol in indoor air and the long-term effects of propylene glycol and glycerol exposure on humans must also be done in order to ascertain if, indeed, the major components of HTP aerosols are harmless.

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DECLARATION OF COMPETING INTEREST

The author is an independent environmental consultant and is not connected to any companies that market or produce tobacco products.

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