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6.1.6 Conclusions on Health Risk of the Tobacco Product

The health risks of cigarette smoking and the risk reductions upon smoking cessation are well described based on a large body of epidemiological evidence [Section 6.5.3.2]. In combination, this knowledge constitutes the points of reference to which the risk modification of switching from cigarettes to THS can be gauged.

As smoking-related diseases are caused by chronic exposure to cigarette smoke constituents, reductions in the levels of harmful and potentially harmful constituents (HPHCs) are in turn expected to lead to reduced disease risks although the degree of risk reduction cannot be directly derived from levels of HPHC reduction.

6.1.6.1 THS compared with cigarettes

Assessing the risks of THS use, relative to smoking cigarettes, is based on multiple studies on HPHC formation, aerosol chemistry, exposure *in vitro*, exposure reduction *in vivo*, and clinical studies. Compared with the Kentucky Reference Cigarette (3R4F), HPHC levels in THS aerosol were reduced by 62% to 99% for both THS variants, i.e. THSR and THSM [Section 6.1.1 Aerosol Chemistry, Tables 4, 6]. THS aerosol compared with cigarette smoke levels of the 18 HPHCs which are subject to reporting on the FDA's abbreviated list (FDA (Food and Drug Administration) 2012) were lower by more than 88% on a per mg nicotine basis to more than 92% on a per stick basis. Compared with a selection of commercial cigarettes (Counts 2006), levels were lower by more than 91% on a per mg nicotine basis to more than 94% on a per stick basis, for both THS variants [Section 6.1.1]. These reduced levels of HPHCs in THS aerosol compared with those measured in cigarette smoke support an expectation that using of THS leads to reduced exposure to these HPHCs and lower health risks compared with cigarette smoking.

In vitro cytotoxicity of gas and particulate phases assessed in pre-clinical studies in both THS variants was lower by more than 90% compared with 3R4F cigarette smoke [Section 6.1.2.2.1]. Likewise, bacterial and mammalian cell mutagenicity was either lower or not observed [Sections 6.1.2.2.2; 6.1.2.2.3]. To induce monocyte-endothelial cell adhesion at levels observed upon direct and indirect cigarette smoke extract exposure, 10 and 20 times higher THS aerosol extract concentrations were required, respectively. [Section 6.1.4.4.1.1].

THS aerosol extract was, compared with 3R4F cigarette smoke extract, approximately 50 times less effective in inhibiting chemotaxis and about 18 times less effective in slowing transendothelial migration (TEM) [Section 6.1.4.4.1.1]. In contrast to 3R4F cigarette smoke extract exposure there was no evidence of reactive oxygen species (ROS) formation in cells exposed to THS aerosol extract and gas vapor phase. THS aerosol total particular matter-dependent increase in DNA damage occurred at doses far exceeding those of 3R4F cigarette smoke total particular matter, and no increase in γH2AX-positive cells resulted from THS gas vapor phase or aerosol extract exposure [Section 6.1.4.4.1.2]. These results indicate a lower potential to induce *in vitro* cytotoxicity, oxidative, and genotoxic stress [Section 6.1.4.4.1.1].

In vivo histopathology showed that respiratory tract irritation and inflammation were either lower in severity or not observed upon THS aerosol compared with 3R4F cigarette

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smoke exposure [Section 6.1.2.3]. In addition, *in vivo* models showed a lower extent of inflammatory changes in the epithelium of the nose, larynx, trachea and lung in rats upon THS aerosol exposure than to what was seen after exposure to 3R4F cigarette smoke. Furthermore, THS aerosol exposure did not alter the total number of free lung cells in the broncho-alveolar lavage fluid (BALF). Quantification of BALF inflammatory mediators demonstrated lower or absent release of mediators into this lung compartment upon THS aerosol exposure compared with 3R4F cigarette smoke, and untargeted proteomics of nasal epithelia similarly revealed a lower differential protein expression. In contrast to what was found at the end of the 3R4F cigarette smoke exposure, *in vivo* effects disappeared in THS aerosol-exposed rats during the recovery period [Section 6.1.4.4.1.2].

These pre-clinical findings unanimously point towards a reduced toxicity of the THS aerosol compared with 3R4F cigarette smoke. Likewise levels of biomarkers of exposure to a certain number of HPHCs in smokers were broadly lower under THS use compared with cigarette smoking in reduced exposure clinical studies ZRHR-REXC-03, ZRHR-REXC-04, ZRHM-REXA-07, and ZRHM-REXC-08. Relative to cigarette smoking, average THS biomarker of exposure levels ranged from 4% to 53% in 5 day confinement periods and from 7% to 67% after 90 days of ambulatory use of both THSM and THSR, in Japanese, European, and US study populations (values exclude S-BMA as the assay could not discriminate smoking from non-smoking, no differences were noted upon use of THS, cigarette or smoking abstinence [Section 6.1.3]).

Clinical risk marker levels were, in line with these findings, found favorable under THS compared with CC consumption, measured after 90 days of use in two studies (ZRHM-REXA-07 and ZRHM-REXC-08). Levels of s-ICAM, a marker of endothelial dysfunction, were lower with THS use by 8% and 10%, respectively; oxidative stress clinical risk marker 8-epi-PGF2α was lower by 12% and 13%, and levels of platelet activation marker 11-DTX-B2 by 5% and 3%. THS group WBC counts were lower relative to smoking at most time points, and lipid metabolism markers levels were found independent of exposure, including in smoking abstinence. Predicted forced expiratory volume in 1 second (FEV_1) was improved by 1.91% in the Japanese study (ZRHM-REXA-07-JP) after 90 days of THS use relative to continued cigarette smoking. In the US study (ZRHM-REXA-08-US), vital capacity was higher by 0.10L relative to smoking. [Section 6.1.4.4].

At the same time THS was generally well tolerated across studies, consistent with results of heat not burn products of the same class. In a study on a carbon heated tobacco product, the proportion of subjects reporting AEs was 50% compared with 54% and 46%, in the CC and SA arm, respectively. Headache was the most common AE, accounting for 23% and 29%, and 14% of AEs in these arms (Ludicke 2016). In three Japanese studies investigating third-party heated tobacco products (Miura 2015, Miura 2013, Sakaguchi 2014) AEs were reported in 25%, 10% and 13% of subjects, and very limited numbers of product-related AEs were observed.

6.1.6.2 Switching from cigarettes to THS

Assessing the changes in risk for THS users switching from smoking cigarettes is based on *in vivo* and clinical studies. Based on the abundantly demonstrated favorable effects

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of exposure to THS aerosol compared with smoking cigarettes, consistent changes in levels of biomarkers of exposure as well favorable changes in clinical risk endpoints were expected upon switching from cigarettes to THS.

In *Apoe*$^{-/-}$ mice switching to THS exposure for 6 months, after 2 months of 3R4F cigarette smoke exposure, led to less inflammation, and reduced, or no perturbations of biological mechanisms were seen in THS aerosol- compared with 3R4F cigarette smoke-exposed animals [Section 6.1.4.4.1.2].

In line with *in vivo* results, levels of biomarkers of carcinogens [FDA definition reported in Section 6.1.3.1 table 2] reduced in clinical studies in smokers switching to THS from baseline cigarette smoking by - 40% to - 94% in confinement, and by - 20% to - 92% under subsequent ambulatory use; levels of Total NNAL, a marker of exposure to tobacco-specific nitrosamines, were reduced by - 48 to - 60% in confinement and by - 67% to - 68% under ambulatory use (ZRHR-REXC-03-EU, ZRHR-REXC-04-JP, ZRHM-REXA-07-JP and ZRHM-REXA-08-US). CYP1A2 activity reduced by - 20% to - 31% (ZRHM-REXA-07-JP and ZRHM-REXA-08-US).

Urine mutagenicity median levels in smokers reduced, upon switching to THS, compared with baseline, by - 42% to - 72% in confinement (ZRHR-REXC-03-EU, ZRHR-REXC-04-JP, ZRHM-REXA-07-JP and ZRHM-REXA-08-US) and by - 61% under ambulatory use in both ZRHM-REXA-07-JP and ZRHM-REXA-08-US. The ranges of reductions were comparable to those attained upon abstinence (- 37% to - 74%, and - 45% to - 67%, in confinement and ambulatory settings, respectively), these findings are in line with results of bacterial and mammalian cell mutagenicity which were either lower, or not observed, in studies comparing exposure to THS aerosol with 3R4F cigarette smoke exposure [Sections 6.1.2.2.2; 6.1.2.2.3].

Biomarkers of exposure to cardiovascular toxicants were, on average, reduced from baseline by - 47% to - 92% in confinement and by - 37% to - 81% after 3 months of ambulatory use of THS. Exposure to respiratory toxicants was reduced from baseline by - 47% to - 86% and by - 37% to - 76% under confinement and ambulatory use, respectively. Exposure to reproductive and development toxicants was reduced by - 49% to - 92% under confinement and by - 39% to - 73% under ambulatory use [Section 6.1.3].

Clinical risk markers were overall also favorably changed from baseline, upon 90 days of THS use in studies ZRHM-REXA-07, and ZRHM-REXC-08; HDL-C improved, on average, by 6% and 8%, respectively and WBC counts were reduced by -4% and -10%. sICAM-1 concentrations decreased by - 13% and - 6%, oxidative stress clinical risk marker 8-epi-PGF2α median levels were changed by - 2% and 1%, and median levels of 11-DTX-B2 by - 18% and - 22%, in ZRHM-REXA-07, and ZRHM-REXC-08, respectively [ZRHM-REXA-07, ZRHM-REXC-08, Appendixes 15].

These findings of favorable biomarker level changes indicate, consistently across studies and across different study populations, that THS use changed the effect of exposure to HPHCs as of the first days after switching to THS. In general, the observed reductions stabilized thereafter, until the end of study, whereas continued cigarette smoking generally resulted in no changes.

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6.1.6.3 THS versus smoking abstinence

In addition to the direct comparison of THS versus cigarette exposure effects and to the changes seen upon switching from cigarettes to THS, another relevant assessment regards the magnitude of the switching effects compared to those of quitting.

No differences were noted in oxidative stress biomarkers in *Apoe*$^{-/-}$ mice switched from cigarette smoke exposure to THS aerosol compared with those switched to air. Similarly, total cholesterol decreased to similar levels upon switching to THS aerosol exposure and to exposure cessation. In mice switched to either air or THS aerosol, plaque areas were smaller than in 3R4F cigarette smoke-exposed mice at 3 and 8 months, although the plaques remained larger than those of sham or long-term THS aerosol-exposed mice. Both switching to THS aerosol and cessation resulted in the stabilization of P-V loops, while continued 3R4F cigarette smoke exposure led to further decline in lung function [Section 6.1.4.4.1.2].

In clinical studies, after smoking abstinence, both in confinement and in the subsequent ambulatory period, compared with baseline biomarker levels reduced by - 35% to - 96%, and - 26% to - 86%, respectively, for carcinogens; by - 64% to - 91% (confinement) and by - 27% to - 75% (ambulatory) for cardiovascular toxicants; by - 58% to - 86% and - 35% to - 79% for respiratory toxicants, and by - 49% to - 91% and - 27 % to - 75% for reproductive and development toxicants (ZRHR-REXC-03-EU, ZRHR-REXC-04-JP, ZRHM-REXA-07-JP and ZRHM-REXA-08-US) [Section 6.1.3].

Table 1 provides a head-to-head comparison of the ranges of reductions of HPHCs upon switching to THS compared with smoking abstinence.

Table 1 Biomarker of exposure to HPHCs ranges of change from baseline, following 90 days of THS use versus Smoking Abstinence

FDA HPHC risk classification	THS (90 days)	SA (90 days)
Carcinogens [a]	-20% to -92%	-26% to -86%,
Cardiovascular toxicants [b]	-37% to -81%	-27% to -75%
Respiratory toxicants [c]	-37% to -76%	-35% to -79%
Reproductive/development toxicants [d]	-39 % to -73%	-27 % to -75%

Average percent changes from baseline. Abbreviations: HPHC = harmful and potentially harmful constituents; THS =Tobacco Heating System; SA: smoking abstinence.
a) 1,3-butadiene, benzene, benzo(a)pyrene, 4-aminobiphenyl, 1-aminonaphthalene, 2-aminonaphthalene, o-toluidine, acrylonitrile, ethylene oxide, crotonaldehyde, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), nitrosonornicotine(NNN),
b) Acrolein, benzene, 1,3-butadiene,
c) Acrolein, acrylonitrile, ethylene oxide,
d) Carbon monoxide, 1,3-butadiene, benzene, ethylene oxide.

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Evidently, after 90 days of ambulatory use, most biomarker of exposure levels reduced in subjects switching to THS to levels close to those seen upon smoking abstinence. Exceptions were 3-HPMA, total NNN and o-toluidine, which in some instances were not reduced as strongly as upon quitting, although the levels were reduced compared with cigarette smoking [Section 6.1.3]. Overall, this indicates that THS exposure effects are closer to what was observed under cessation than under continued cigarette smoking.

At the same time, withdrawal symptoms were reported being higher during abstinence than for both CC and THS conditions. Thus, in addition to reductions in exposure as well as in exposure effects upon using THS compared with smoking, THS has the potential to provide adult smokers with an acceptable alternative to cigarettes.

While average body weight remained unchanged in all 3 arms in ZRHM-REXA-08-US [Section 6.1.5.4.3] it increased by 2.5 kg in the abstinence arm while it remained unchanged in both the THS and the CC arms of the Japanese 3 months study (ZRHM-REXA-07-JP).

Based on the reported effects of switching to THS, approaching what occurred upon cessation, one implication related to medical drugs is worthwhile pointing out. The pharmacokinetic and pharmacodynamic effects of certain medicinal drugs might be expected to be impacted in ways similar to what results from smoking cessation [Section 6.1.5.5.2]; dosage adjustments for certain medical drugs might thus be indicated with THS use as well.

6.1.6.4 Multiple products and nicotine replacement

Assessments of risks of dual or poly-use were drawn based on adverse events observed in clinical studies. The assessment of THS compared to tobacco cessation medication use is based on literature data. The aforementioned evidence on reduced exposure, toxicity, biomarkers of exposure, and clinical risk markers does not include results on long-term health outcomes, including on disease risks or risk reductions. This is inevitable, as the duration and prevalence of use of THS does not yet allow for measuring such endpoints through epidemiological health-outcomes studies. Similarly, clinical endpoint results, presented by various levels of dual use, will only be available as the PMI clinical assessment program progresses, but are not, and cannot be, available to date. The only exception to this is data on acute safety. A review of adverse events shows that predominant THS users (70%+ THS use) had similar AE rates as cigarette smokers (47.8% vs. 35% in ZRHM-REXA-08-US and 36.6% vs. 34.1% in ZRHM-REXA-07-JP). Dual users (30% to 70% THS use) had higher AE rates (60% in both studies) and full abstainers had smaller rates (16.7% and 22.7%), although these figures are based on small sample sizes [Section 6.1.5.2.2.3]. Cough data observed in the abstinence arm of the US 3 months study (ZRHM-REXA-08-US) suggest that smoking less than 3 cigarettes a day did not alter the pulmonary short-term benefits, while dual users smoking 5+ cigarettes a day may experience more coughing, although this remains to be confirmed with post market data [Section 6.1.5.4.4].

While favorable exposure, toxicity, biological response, and clinical risk endpoint effects of THS use over cigarette smoking have been demonstrated consistently across a large number of studies, populations and endpoints [Sections 6.1.1 to 6.1.4], the question as to

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how THS would compare with FDA-approved tobacco-cessation medication is worthwhile considering.

A comparative review of nicotine replacement therapy (NRT) studies claims that the chances of stopping smoking for 6+ months after cessation were increased by 50% to 70% by NRTs (Stead 2012). However, as recently published, the NRT advantage disappeared after adjustment for sources of potential biases (Stanley 2016). Moreover, the Tobacco Advisory Group of the Royal College of Physicians concluded that "there is little or no difference in the likelihood of quitting", referring to unaided compared with NRT-supported quitting attempts (Royal College of Physicians 2016) (p.100). Thus, in the case of a lack of effectiveness of NRTs, the health risks of smokers attempting NRT-supported quitting compare essentially with those of smokers trying to quit without NRT support. As demonstrated in Sections 6.1.1 to 6.1.4 of this dossier, THS-related health risks are in all likelihood lower than those related to smoking. This renders THS very likely the best alternative for smokers unwilling to quit, irrespective of NRTs.

6.1.6.5 THS versus never exposure

The assessment of health risks of initiating the use of THS compared to never using tobacco products is restricted to *in vitro* and *in vivo* studies. Even though the amount of evidence of favorable THS effects in comparison to cigarette smoking summarized above builds on the two goalposts of continued cigarette smoking on one hand and (successful) quitting on the other, the question can be raised as to how THS would compare with never using tobacco products in the first place. In non-smoking humans, measurements of effects of tobacco product use are not feasible for ethical reasons. However, such studies *in vitro* and in animals can be, and in fact were, conducted.

THS aerosol exposure caused negligible *in vitro* cytotoxicity, tissue damage, and secretion of inflammatory mediators in 3D human oral, nasal and bronchial epithelial tissues, closer to what was observed upon exposure to air than to what was measured upon exposure to 3R4F cigarette smoke [Section 6.1.4.4.1.1].

In rats, lung inflammation was evident upon exposure to 3R4F cigarette smoke, but not following exposure to THSR and THSM aerosol [Section 6.1.2.3]. Changes in organ weights in all exposure arms included increased liver weight, an expected nicotine-related side effect (Phillips 2015), and increased adrenal gland weight following THS aerosol exposure, while the weights of the thymus and the uterus decreased.

With respect to inflammatory endpoints in the *Apoe*-/- mouse study, such as the extent and severity of pigmented macrophage nests and the degree of inflammatory cell infiltration, there were no significant differences between the sham controls and THS aerosol-exposed mice at any time point. Relative to values in sham mice, prolonged exposure to the THS aerosol had no effect on total free lung cell counts. The inflammatory mediator concentrations in the broncho-alveolar lavage fluid (BALF) of THS aerosol-exposed mice were very similar to those in BALF samples obtained from sham animals [Section 6.1.4.4.1.2.2].

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6.1.6.6 Overall Evaluation

The smoke chemistry findings demonstrate reductions in the levels of measured HPHCs in THS aerosol compared with those in cigarette smoke. Also, cytotoxicity, genotoxicity and histopathology effects were lower. Lower biomarker levels were found consistently across clinical studies with THS use compared with cigarette smoking, indicating smaller biological effects. In line with these findings, levels of markers of clinical risk turned out favorable across clinical studies, supporting lower adverse health impacts of THS use compared with cigarette smoking.

The changes related to switching from cigarettes to THS were in line with the findings from comparisons of THS use relative to cigarette smoking. This was the case for biomarkers of HPHCs known to be carcinogenic as well as for those related to cardiovascular, respiratory, reproductive and developmental toxicants. Furthermore, the changes in clinical risk endpoints were favorable and consistent with reduced HPHC exposure levels, and changes in clinical risk endpoints of smoking-related disease pathways shifted in the direction seen upon smoking abstinence. The evidence indicates reversibility of cigarette smoking exposure effects, including effects in clinical risk markers. The findings obtained are in line with what would be expected upon switching to a reduced risk product. At the same time the rate and amount of nicotine uptake from THS was comparable to that from cigarettes [Section 6.2.1.1].

In general, the magnitude of the differences of exposure effects found from comparing THS and cigarettes as well as the size of effects of switching from cigarette smoking to THS, including those observed in relevant biomarkers, were largely in line with the findings observed upon smoking abstinence. Also, compared with unsuccessfully attempting smoking cessation with or without nicotine replacement therapy, THS is almost certainly a viable and advantageous alternative for smokers unable to quit.

The effects of various levels and durations of dual use on health outcomes require post-market research in sufficiently large populations of THS users. Available data indicate that concomitant use of no more than three cigarettes per day may not substantially alter pulmonary benefits compared with continued cigarette smoking. Post market research must also be conducted to quantify effects of THS initiation in never smokers. As the totality of the available evidence indicates, any potential adverse health effects in that group can be expected to be far below what is known to result from initiating cigarette smoking.

The PMP product assessment program shows that switching exclusively to THS presents less risk of harm compared to continuing to smoke cigarettes. Therefore if sufficiently widely accepted and used by adult smokers, THS can reduce population harm compared with smoking.

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6.1.6.7 References

Counts ME, Hsu FS, Tewes FJ. Development of a commercial cigarette "market map" comparison methodology for evaluating new or non-conventional cigarettes. Regul Toxicol Pharmacol. 2006; 46(3):225-42.

FDA (Food and Drug Administration). Guidance for industry - Reporting harmful and potentially harmful constituents in tobacco products and tobacco smoke under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act - Draft guidance. 2012.

Ludicke F, Haziza C, Weitkunat R, Magnette J. Evaluation of biomarkers of exposure in smokers switching to a carbon-heated tobacco product: a controlled, randomized, open-label 5-day exposure study. Nicotine Tob Res. 2016.

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

Miura N, Yuki D, Minami N, Kakehi A, Onozawa M. Pharmacokinetic analysis of nicotine when using non-combustion inhaler type of tobacco product in Japanese adult male smokers. Regul Toxicol Pharmacol. 2013; 67(2):198-205.

Phillips B, Esposito M, Verbeeck J, Boue S, Iskandar A, Vuillaume G, Leroy P, Krishnan S, Kogel U, Utan A, Schlage WK, Bera M, Veljkovic E, Hoeng J, Peitsch MC, Vanscheeuwijck P. Toxicity of aerosols of nicotine and pyruvic acid (separate and combined) in Sprague-Dawley rats in a 28-day OECD 412 inhalation study and assessment of systems toxicology. Inhal Toxicol. 2015; 27(9):405-31.

Royal College of Physicians. Nicotine without smoke: tobacco harm reduction. A report by the Tobacco Advisory Group of the Royal College of Physicians. London: RCP. 2016.

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

Stanley TD, Massey S. Evidence of nicotine replacement's effectiveness dissolves when meta-regression accommodates multiple sources of bias. J Clin Epidemiol. 2016.

Stead LF, Perera R, Bullen C, Mant D, Hartmann-Boyce J, Cahill K, Lancaster T. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev. 2012; 11:CD000146.

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