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6.4 Effect of Marketing on Consumer Understanding and Perceptions

6.4.1 Background and Overview

As reflected in the FDA MRTP Draft Guidance (FDA (Food and Drug Administration) 2012), the effect that an MRTP's marketing will have on consumer understanding and perception is an important consideration: "*All MRTPAs must contain evidence to show that the advertising and labeling concerning modified risk products enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all of the tobacco-related diseases and health-related conditions associated with the use of tobacco products.*" (lines 788-793, FDA (Food and Drug Administration) 2012).

To have a predictable public health benefit, accurate and scientifically substantiated information about the modified risk of THS need to be communicated to consumers. Risk/benefit communication plays a crucial role in helping adult smokers elect to use an MRTP. Without such communication, the incentive for adult smokers to adopt an MRTP to lessen risk is likely to be low, and the chances for individual-level harm reduction are reduced. Equally important is that communication on harm reduction does not have unintended consequences, including increasing uptake of tobacco among never smokers, encouraging former smokers to take up tobacco again, or discouraging cessation among smokers motivated to quit.

This section of the application summarizes the premarket evidence collected to gain insight into the impact of *THS labeling and advertising* ('THS communication') on consumer understanding and perceptions. Specifically, this section focuses on how users and non-users of CC understand different modified risk information communicated on THS and how this relates to their risk perception of using THS.

To assess consumer understanding and perceptions of the marketing of an MRTP, the IOM recommends the adoption of a multi-stage approach that includes qualitative and quantitative studies (IOM (Institute of Medicine) 2012). Specifically, The IOM recommends to start with qualitative research to help determine the most accurate and easily comprehended message and to conclude with quantitative research to test the effects of verbal and non-verbal elements of the MRTP labeling and advertising on consumer understanding and perception (p.8, IOM (Institute of Medicine) 2012). Furthermore, the FDA MRTP Draft Guidance recommends to test several variations of the proposed claim on labels and/or in advertisements (lines 1044 to 1046, FDA (Food and Drug Administration) 2012).

In order to develop clear, accurate, and effective communication about THS, a Perception and Behavior Assessment (PBA) program that addresses the FDA's recommendations, was initiated. One of the objectives of this program was to develop communications for THS that:

- Enable the public to comprehend information concerning modified risk
- Effectively communicate the risks associated with THS in comparison to CC, NRTs and Cessation

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As summarized in Table 1, a total of 6 studies were completed to respond to FDA's requirements on the effect of THS on consumer understanding and perceptions. These studies included qualitative and quantitative studies of either of 2 phases:

(1) **Development phase**: 2 qualitative studies ([THS-PBA-02-US] and THS-PBA-04-US) and 1 quantitative study [THS-PBA-03-US] to guide the development of the most appropriate THS communication
(2) **Assessment phase:** 3 quantitative studies ([THS-PBA-05-RRC-US], [THS-PBA-05-RRC2-US], and [THS-PBA-05-REC-US]) to assess the appropriateness of proposed THS label, labeling, and marketing material submitted in this application.

In addition to *Comprehension and Risk Perception assessment* conducted in these 6 studies, *Intent to Use THS* was assessed in adult current CC smokers (Section 6.2.2) and in adult non-tobacco users (both former and never users; Section 6.3.1). *Change in Intention to Quit Smoking* within adult smokers was also assessed in the quantitative studies (Section 6.2.2).

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Table 1 Overview of the Studies

Study Name	Study Type	Cities	Study Period	Study Population	Age of Participants	THS Communications
THS-PBA-02-US	Qualitative	Boston, MA Chicago, IL Charlotte, NC Phoenix, AZ	Oct-Dec 2013	S-NITQ, S-ITQ, FS, NS[a]	21+	9 potential 'plain text'[b] messages
THS-PBA-03-US	Quantitative	Chicago, IL Marlton, NJ Phoenix, AZ Atlanta, GA	Oct-Dec 2014	S-NITQ, S-ITQ, FS, NS	LA+	3 potential 'plain text'[b] messages selected from THS-PBA-02-US
THS-PBA-04-US	Qualitative	Chicago, IL Phoenix, AZ	Dec 2014	AS, FS, NS	18+	5 potential branded[c] communication materials with claims selected from THS-PBA-02-US
THS-PBA-05-RRC-US	Quantitative	Paramus, NJ Dallas, TX St Louis, MO Los Angeles, CA	Jul 2015	S-NITQ, S-ITQ, FS, NS	LA+	3 branded[c] communication materials with claim #1 "Reduced risks of tobacco-related diseases"
THS-PBA-05-RRC2-US	Quantitative	Marlton, NJ Chicago, IL Tampa, FL Denver, CO	Sep 2015	S-NITQ, S-ITQ, FS, NS	LA+	3 branded[c] communication materials with the claim #2 – "Reduced risk of harm"
THS-PBA-05-REC-US	Quantitative	Framingham, MA San Diego, CA St Louis, MO Baltimore, MD	Dec 2015	S-NITQ, S-ITQ, FS, NS	LA+	3 branded[c] communication materials with the claim #3 "Reduced body's exposure to harmful and potentially harmful chemicals"

Abbreviations.: AS = Adult Smokers; CC = Conventional Cigarettes; FS = Adult Former Smokers; HPHC = Harmful and Potentially Harmful Constituent; IDI = Individual Interviews; LA = Legal Smoking Age; NS = Adult Never Smokers; S-ITQ = Adult Smokers with the Intention to Quit; S-NITQ = Adult Smokers with no Intention to Quit;

[a] Never Smokers participated only in Phase 2 of THS-PBA-02-US.

[b] 'plain text' message describes the information communicated on the product

[c] The branded communication materials are THS label, labeling and marketing material. THS device was presented with *iQOS* commercial name and the Tobacco Sticks as *HeatSticks* with the *Marlboro* Brand.

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6.4.2 Overall Approach

6.4.2.1 THS Communication

PMI's MRTP assessment strategy builds on a broad range of data from non-clinical to clinical studies to assess the extent to which THS produces reduced levels of HPHCs, presents a reduced toxicological profile, reduces the exposure to HPHCs and ultimately reduces the individual risk of tobacco-related diseases compared to continued smoking. Based on the weight of evidence substantiated by nonclinical and clinical data in support of this MRTPA, several communications based either on reduced risk or reduced exposure information were crafted for the development phase. Two main elements pertaining to THS communication are considered in the PBA studies: (i) *the Product Message,* which describes the information communicated on the product and (ii) *the Communication Materials,* which deliver the product information in designated communication channels (e.g., pack, brochure, and printed advertising).

Product Message. The Product Message is designed to include a variety of information concerning THS features, risks, potential benefits ('claimed effects') and intended consumers. Important insights on how to appropriately structure THS Message (wording, amount of information, order of information, framing) were gained from preliminary research conducted outside of the US prior to engaging in the PBA program. This baseline understanding was the basis of the potential messages to test on US consumers in [THS-PBA-02-US]. The content of a THS Message follows this general structure:

- **Information Section**: A general description of THS and a description of how THS works
- **Intended Users Section**: Statements of the intended users of THS
- **Available Evidence to Date Section**: Statements on the benefits of THS relative to smoking conventional cigarettes, including a modified risk claim
- **Important Warning**: Statements on the risks inherent to use of THS

Communication Materials. Three main categories of Communication Materials were developed by Philip Morris USA[1] (PM USA), in consultation with PMI to market THS in the US:

- THS "*label*" refers to the display of printed text or graphical material, including branding, on the pack containing THS Tobacco Sticks, or the packaging box of the THS Main Unit.
- THS "*labelin*g" refers to printed or graphical material which accompanies THS. For example, labeling could refer to (i) brochures, (ii) leaflets inserted into the packaging of the THS Main Unit or the pack of THS Tobacco Sticks, and (iii) other similar text which is not printed on the pack but is on the materials accompanying the pack.

[1] Although PMP S.A. is submitting this MRTP application and is asking FDA for a modified risk order, PMP S.A. has entered into an agreement with Altria Client Services LLC ("ALCS")[1] by which ALCS or an affiliate has a license to distribute and sell the THS system in the United States. The ALCS affiliate that will distribute and sell the THS system is Philip Morris USA ("PM USA").

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- THS "*marketing material*" refers to promotional material or any advertising, such as point of sale advertising.

Section 4 presents in detail the Communication Materials submitted with this application. These materials include (i) the *Pack* containing THS Tobacco Sticks, (ii) the THS *Brochure* and (iii) an advertising mail with a (b) (4) (b) (4) also known as THS *Direct Mail*. These Communication Materials were first examined qualitatively in [THS-PBA-04-US] among other materials, and then tested quantitatively in 3 studies [THS-PBA-05-RRC-US], [THS-PBA-05-RRC2-US], [THS-PBA-05-REC-US] to obtain evidence on comprehension and risk perception. These materials employ different layout, and represent different channels of communication with different purposes. Therefore, it is important to assess all of them to ensure that they will consistently generate the same understanding and perceptions among both current smokers and non-smokers. It is well established that health warnings on tobacco packages are among the most direct and prominent means of communicating with smokers (Mutti 2011). Likewise, health-related information on THS should come across in a simple and straightforward manner on the pack label for consumers to understand the key information. In contrast, the *THS Brochure* aims at educating adult smokers on THS, including on what THS is and how it differentiates from conventional cigarettes and e-cigarettes. The *Direct Mail* is the most promotion-oriented communication and aims at generating awareness and facilitating opportunity to try THS among current adult smokers.

6.4.2.2 Types of Studies

6.4.2.2.1 Qualitative Studies

As recommended by the IOM in its report (IOM (Institute of Medicine) 2012), qualitative studies are particularly useful to perform formative and exploratory work in a developmental phase. Those studies were helpful in generating a broad understanding of various subpopulation reactions to different types of communication or variations of similar concepts. In particular, qualitative research supported the understanding of how different elements of a potential communication (e.g., wording, tone of written language, amount of information, order of information, and framing) contribute to the overall consumer understanding of the information related to modified risk. Focus group discussions (FGDs) and individual interviews (IDIs) were used in [THS-PBA-02-US], while only IDIs were used in [THS-PBA-04-US].

6.4.2.2.2 Quantitative Studies

The quantitative studies, [THS-PBA-03-US] in the development phase and [THS-PBA-05-RRC-US], [THS-PBA-05-RRC2-US], [THS-PBA-05-REC-US] in the assessment phase, were conducted in large samples of adult smokers and adult non-smokers using a 5-arm parallel-group experiment to quantify *Comprehension* of THS communication and the *Risk Perception* associated with THS usage in comparison to CC, E-cigarettes, NRTs and Cessation. The 5 arms corresponded to 5 different THS Messages for [THS-PBA-03-US], and to 5 instances of THS label, labeling and marketing material for [THS-PBA-05-RRC-US], [THS-PBA-05-RRC2-US], [THS-PBA-05-REC-US]. In these studies, subjects were first exposed to an instance of THS communication and then presented with a

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battery of assessments administered in a fixed order using computer-assisted self-interview (CASI) methodology to ensure consistency in the presentations of questions across interviews.

Comprehension Assessment

Comprehension was quantified based on the responses of subjects to a series of closed-ended questions in order to test consumers' ability to accurately understand the Message's communication objectives regarding the relative risks, benefits from switching completely from CC to THS, and conditions of using THS. The comprehension assessment was designed based on label comprehension testing methodology used mainly in prescription–to-over-the-counter drug-switch research to provide diagnostic information on consumers' ability to accurately understand communication objectives included in a product fact sheet (FDA (Food and Drug Administration) 2010, Morris 1998).

The quantitative studies assessed 2 types of comprehension:

(1) **Global Comprehension:** overall comprehension of the communication objectives regarding the exposure to harmful of potential harmful constituents (HPHCs) and the risk related to switching completely from CC to THS
(2) **Specific Comprehension**: comprehension of specific parts of the THS communication (e.g., the intended users of THS, available evidence to date, warning statements)

Both types of comprehension were assessed with multiple-choice questions, 5 response options were presented, with 1 correct option, 3 incorrect options and an option for "don't know".

Risk Perception Assessment

It has been acknowledged that valid methods to assess risk perception of tobacco products are still lacking, though this is key to provide the needed empirical basis for future MRTP assessment and regulation (Rees 2009). No psychometrically sound self-report instrument exists, which would allow for comparing, on the one hand, perceived risks of an MRTP relative to other tobacco and non-tobacco products, and on the other hand, perceived risks in populations with different smoking status. To fill this gap and as part of this PBA program, the psychometric development of a risk perception instrument, the *Perceived Risk Instrument (PRI)*, was undertaken according to best practice guidelines, including the current FDA guidance for patient-reported outcomes (PROs) in clinical trials (FDA (Food and Drug Administration) 2009, Revicki 2007, Scientific Advisory Committee of the Medical Outcomes Trust 2002). The approach to develop and validate this instrument is described in more detail in [A732 PBA01Sum]. The PRI aims at quantifying consumers' perceived risks of using various types of tobacco and nicotine-containing products as well as the perceived risks associated with the past use of CC (e.g., after successfully quitting smoking, referred to as "cessation" in this context). The instrument includes an 18-item *Perceived Health Risk scale* and a 7-item *Perceived Addiction Risk scale*, complemented by 2 single items assessing *Perceived Harm to Others*(full list of the PRI items available in [A732 PBA01Sum]).

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6.4.2.3 Study Population

For all PBA studies, the target population was adults living in the United States. The sampling frame consisted of adults living in strategically selected areas forming a geographically diverse sample, such that each city was within the 4 regions defined by the United States Census Bureau (Table 1). Subjects participating in PBA studies were recruited via telephone by independent vendors using proprietary databases.

Main Sample

The Main Study Samples were comprised of both adult smokers and adult non-smokers based on subjects' self-report of tobacco use as follows:

(1) **Adult Smokers with no Intention to Quit CC**[2]:
Current adult smokers having smoked at least 100 CC, are currently smoking CC, and having no intention of quitting as defined by Prochaska and DiClemente's Stages of Change Model ("pre-contemplation" stage) (Prochaska 1982).

(2) **Adult Smokers with the Intention to Quit CC**[1]:
Current adult smokers having smoked at least 100 CC , and having the intention to quit CC as defined by Prochaska and DiClemente's Stages of Change Model ("contemplation" and "preparation" stages) (Prochaska 1982).

(3) Adult Never Smokers:
Adults having either never smoked at all, or never having been daily smokers and having smoked less than 100 CC.

(4) Adult Former Smokers:
Adults having formerly been daily smokers (i.e., having smoked at least 100 CC) and, at the time of study, having quit smoking CC more than 30 days ago. In addition, in all quantitative studies, a minimum quota of subjects who have had quit smoking over at least a total of twelve months ("long-term quitters") was used to ensure a sufficient number of people whose quitting was more long term was represented in the studies (approximately 30%).

Oversample of Young Adults Never Smokers

In all quantitative studies (i.e. [THS-PBA-03-US], [THS-PBA-05-RRC-US], [THS-PBA-05-RRC2-US], and [THS-PBA-05-REC-US]), an oversampling of young Adult Never Smokers, was recruited to approximate the same number of participants from each smoking group in the Main Sample. This intentional oversampling of young adults provided sufficient data to adequately describe responses within this younger group and thus allows for inferences on the understanding and perception of the product messages and marketing materials in non-adults (PMI internal policy prohibits the conducting of studies relating to tobacco products involving minors). This is in line with the recommendations from the FDA, as stated in its preliminary responses to PMI meeting request STN: TC0000737 sent on September 3, 2013: "*FDA does not believe that it is*

[2] In PBA developmental studies, only Regular Smokers (smoking at least 1 CC a day) were included. PBA assessment studies included between 10% and 40% of Intermittent Smokers (smoking on between 4 and 27 days per month, with no restrictions on total number of CC smoked in that period).

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necessary for applicants to conduct research with non-adult populations. However, FDA recommends that applicants provide information about the likely impact that marketing a product as modified risk may have on non-adults and their tobacco use behavior. This information may be inferred from studies with other similar populations, such as young adults." (P.004).

(5) Legal Smoking Age to 25 years of age (LA-25) Never Smokers:

Young adults between legal smoking age and 25 years of age, who, based on self-report information, having either never smoked at all, or never having been daily smokers and having smoked less than 100 CC.

6.4.3 Development Phase

This section reports only the major results related to *Comprehension* and *Risk Perception* of the 3 studies included in the Development Phase. More detail can be found in the summary and full report of the individual studies in Section 7.3.2.

6.4.3.1 THS-PBA-02-US Study

The main purpose of this study was to contribute to the development of THS potential product messages by exploring how each element of different messages contributes to the *comprehension* of the modified risk information, *intent to use* THS, and *risk perception* of THS compared to other tobacco and nicotine-containing products, and to the intention to quit tobacco use.

Methodology

A brief description of the study methods is provided in Table 2.

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Table 2 Methodology of THS-PBA-02-US

Study Title: Qualitative Study to Develop THS 2.2 Hypothetical Product Messages

Study design: 4-cities, 2-phase, sequential, qualitative study.

Phase 1 'Product Message Development' consisted of 1 pilot focus group discussion (FGD) and 20 FGDs, where participants shared their opinions and reactions to a variety of discussion topics in an interactive group setting to contribute to the development and refinement of the THS product messages.

Phase 2 'Product Message Understanding' consisted of 1 pilot individual interview (IDI) and 37 IDIs conducted with the aim of identifying detailed perceptions, opinions, beliefs, and attitudes of participants as well as of evaluating the clarity of the revised product messages resulting from Phase 1.

Subjects: Enrolled: 123 in FGDs and 38 in IDIs; Full analysis population (FAP): 117 in FDGs and 37 in IDIs; Number of adult smokers in the FAP: 93 in FGDs and 25 in IDIs; Number of adult former smokers in the FAP: 24 in FGDs and 6 IDIs; Number of adult never smokers in the FAP: 6 (IDIs).

Main criteria for inclusion:

- Aged 21 or older
- Adult Smokers with no Intention to Quit CC: currently smoking at least 1 CC/day, started more than 30 days ago with no intention to quit within 6 months; Adult Smokers with Intention to Quit CC: currently smoking at least 1 CC/day, started more than 30 days ago with the intention to quit within 6 months ; Adult Former Smokers: quit smoking CC more than 30 days ago; Adult Never Smokers (Phase 2 only): never smoked or never smoked daily and less than 100 CC

Methods: Moderators (5+ years of experience) conducted the FGDs and IDIs. A discussion guide was employed in each FGD and IDI in order to elicit participant feedback in a consistent manner across the various FGDs and IDIs.

Criteria of Evaluation: Verbal data, transcribed from the FGDs and IDIs, were examined for each potential product message in general, and by smoking status in particular, to identify the extent of endorsement.

Different formulations of messages were tested, varying the level of specificity of the claim (general *vs.* specific), type of claim (reduced exposure *vs.* reduced risk), and format (with or without a graph; important warning as a separate box or as part of the message). A summary of the modified risk claims assessed is shown in Table 3 for Phase 1 and Phase 2.

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Table 3 THS Messages tested in THS-PBA-02-US

	Specific Potential Claims	General Potential Claims
Phase 1		
Reduced Exposure	**A**. With THS 2.2, the production of carbon monoxide is reduced by more than 95%	**C**. Switching to THS 2.2 significantly reduces your body's exposure to many harmful chemicals found in cigarette smoke which are identified as likely causes of smoking-related diseases
	B. THS 2.2 produces at least 90% less second-hand smoke than CCs	**D**. THS 2.2 significantly reduces the production of harmful chemicals found in cigarette smoke
Reduced Risk	**E**. Switching to THS 2.2 can lower your cardiovascular disease risks	**H**. Switching to THS 2.2 can lower several risk factors that could lead to smoking-related diseases
	F. Switching to THS 2.2 improves several biomarkers, which are seen as early indicators of emphysema	**J**. Switching to THS 2.2 can reduce risks of smoking-related diseases
	G. Switching to THS 2.2 can improve the level of good cholesterol and can reduce the risk of clogging of arteries due to smoking	
Phase 2		
	Specific Potential Claims	**General Potential Claims**
Reduced Exposure	**B**. THS 2.2 produces an aerosol. Unlike conventional cigarettes, THS 2.2 does not produce smoke or second-and smoke.	**C**. Switching to THS 2.2 significantly reduces your body's exposure to many harmful chemicals found in cigarette smoke which are identified as likely causes of tobacco-related diseases
	L. THS 2.2 significantly reduces the production of harmful chemicals, such as carbon monoxide which is reduced by 95%, found in cigarette smoke	
Reduced Risk	**E**. Switching to THS 2.2 can lower your cardiovascular disease risks	**H**. Switching to THS 2.2 can lower several risk factors that could lead to tobacco-related diseases
	K. Switching to THS 2.2 can improve lung function	**J**. Switching to THS 2.2 can reduce risks of tobacco-related diseases

Data Source: Study Report THS-PBA-02-US Appendix c.

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Results

Below we summarize the key insights from this first qualitative study and show some verbatims for illustrative purposes.

- Participants had a correct understanding that THS is a tobacco product and thus stated that there is a health risk associated with using THS.
- Most adult smokers' comments reflected the idea that the risks associated with using THS are potentially reduced compared to using CC, because the tobacco in THS is heated and not burned.

  "*Because of the reduction in the risk…if their message is designed to give you the satisfaction, flavor and taste of a cigarette, and they're reducing the risk of harmful chemicals, and the probability of reducing diseases, it's a positive message for a smoker. (A positive message for) somebody who's concerned about their health. That's a great idea to heat instead of burn if it has all these benefits, I think it's great."* (Adult smoker, male 51+, Charlotte)

- There was a clear understanding regarding the intended audience for THS, conveyed by the presence of statements "it is not for ex-smokers" and/or "it is not for non-smokers."

  "No other product says it's not for smokers who want to quit, not for ex-smokers, and not for non- smokers. It's pretty right to the point. Anybody that wants to quit smoking, don't waste your time…it's for people who don't want to stop smoking but are looking for an alternative - it's right out there." (Adult smoker, male 51+, Boston P2)

- Participants were more interested in messages related to risk of developing diseases than in the risk of exposure to harmful compounds because the former was perceived as the only concrete way that THS could be demonstrated to be less harmful than conventional cigarettes.
- CC were viewed as having the highest risk because they contain tobacco and generate smoke. E-cigarettes, NRTs, and cessation were viewed as having decreasing levels of risk. THS was perceived as more risky than E-cigarettes and NRTs (because THS contains tobacco), but lower in risk than CC (because the message stated that tobacco in THS is heated and not burned).

  "It says it reduces your body's exposure to harmful chemicals whereas smoking regular cigarettes does not obviously. You are exposed 100% with regular cigarettes no matter what. This says it significantly reduces your body's exposure. That's a grabber for me. And you still feel like you're smoking. You still have the taste and the exhale and all that stuff." (Adult smoker, female, 21-35, Phoenix)

  "e-cigarettes, it's a liquid form whereas the THS is an actual tobacco product…I would say that's probably the reason why, because it's an actual tobacco substance and not just chemical nicotine." (Adult smoker motivated to quit, male, 36-50, Boston)

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Based on this first study, 4 out of the 9 messages (B, C, J, and L, as noted in) were identified both as the best understood messages, as well as the messages that resonated the most for adult current smokers. As expressed by the study participants, these messages shared some common elements and features: (i) they make reference to well-known risks related to tobacco use that are of concern to adult smokers (e.g., second-hand smoke, tobacco-related diseases), (ii) they contain clear and compelling statements supported by statistics or authoritative backing (i.e., "scientific studies"), and (iii) they use simple wording and short, straightforward language that is easily understandable. In particular, the graphic display of information included in Product Message L was perceived as effective, adding credibility and completeness to the product message– even though many of the participants mentioned that they could not fully grasp the details of the chart. Below are verbatims shown for illustrative purposes.

> *"The thing that caught my eye, although we demonstrated that the THS 2.2 produces an aerosol that does not produce smoke or second-hand smoke. It makes me feel better that it is not really producing smoke or second-hand smoke. That kind of caught my attention."* (Adult smoker, female, 21-35, Phoenix)

> *"Because of the reduction in the risk…if their message is designed to give you the satisfaction, flavor and taste of a cigarette, and they're reducing the risk of harmful chemicals, and the probability of reducing diseases, it's a positive message for a smoker. (A positive message for) somebody who's concerned about their health. That's a great idea to heat instead of burn if it has all these benefits, I think it's great."* (Adult smoker, male, 51+, Charlotte)

> *"Not burned, that's very intriguing. Reduce the production of harmful materials in cigarette smoke. Scientific studies. Human nature when you see scientific studies you sort of like give it the more positive than negative."* (Adult smoker, male, 51+, Boston)

> *"I think the Important Warning was just way more blunt and to the point. It just lays it out. No sugar-coating it. It just gives you the facts. Although it reduces risk it's still there."* (Adult smoker, female, 21-35, Phoenix)

In contrast, product messages that were rejected tended to use vague or unfamiliar terms (e.g., risk factors, biomarkers) or used reference to aspects which are not associated with smoking or tobacco use (e.g., improve the level of good cholesterol).

Based on the study findings, 3 communication types based on C, J and L messages (shown in Table 3) were selected and carried over to studies [THS-PBA-03-US] and [THS-PBA-04-US]. In terms of formatting, the "Important Warning" appearing as text outlined in a box was selected over appearing as another text paragraph as it was preferred due to its familiarity as a "warning".

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6.4.3.2 THS-PBA-03-US Study

The overall aim of this study was to further inform the selection of appropriate Product Messages using quantitative assessment of 5 potential "plain text" THS messages in terms of *Intent to Use* THS, *Comprehension* of different communication objectives, *Risk Perception* of THS and the comparators CC, NRTs, E-cigarettes, and Cessation. *Change in Intention to Quit Smoking* within adult smokers was also assessed as part of the Study.

Methodology

A brief description of the study methods is provided in Table 4.

Table 4 Methodology of THS-PBA-03-US

Study Title: Study to Quantitatively Assess THS 2.2 Potential Messages
Study Design: 4-cities, 5-arm parallel-group experiment. The 5 arms corresponded to the 5 different THS messages, each of them being tested by approximately equal numbers of subjects from different smoking status groups.
Subjects: *Full Sample* for analysis: 1713; Number of Adult Smokers with no Intention to Quit CC included in the *Main Sample*: 359; Number of Adult Smokers with Intention to Quit CC included in the *Main Sample*: 355; Number of Adult Former Smokers included in the *Main Sample*: 358; Number of Adult Never Smokers included in the *Main Sample*: 362; Number of Adult Never Smokers from the legal age of smoking to 25 years of age (*LA-25 Adult Never Smokers*) included in the *Full Sample*: 358 (including 79 from the main sample).
Main Criteria for Inclusion: Aged 18 and above, or above state legal smoking age if above 18 years Adult Smokers with no Intention to Quit CC: currently smoking at least 1 CC/day, started more than 30 days ago with no intention to quit within 6 months; Adult Smokers with Intention to Quit CC: currently smoking at least 1 CC/day, started more than 30 days ago with the intention to quit within 6 months; Adult Former Smokers: quit smoking CC more than 30 days ago; Adult Never Smokers: never smoked or never smoked daily and less than 100 CC
Methods: Comprehension Closed questions on Global and Specific Comprehension of THS Product Messages [THS-PBA-03-US Study Report Appendix 16.1.1]. Risk Perception The PRI-Personal Risk (PRI-P) [A732 PBA01sum] composed of 3 domains: Perceived Health Risk measured by an 18-item scale Perceived Addiction Risk measured by a 7-item scale Perceived Harm to Others measured by 2 single items

(table continues)

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Criteria for Evaluation:

Level of Comprehension:

Proportion of subjects correctly answering Comprehension questions, by study arm, for the Main Sample and LA-25 Never Smoker Sample

Risk Perception:

Perceived Health Risk, Perceived Addiction Risk and Perceived Harm to Others for THS and each comparator (i.e., CC, E-cigarettes, NRTs and Cessation), by study arm and smoking status group

Five messages were tested through combinations of 3 claims (selected based on [THS-PBA-02-US] findings) and different warnings. A summary of the different combinations of modified risk claims and warnings assessed in [THS-PBA-03-US] Study are shown in Table 5. The general structure of THS Message was similar across the five messages, with the exception that Message 1 and 2 contained a graphical display of HPHCs reduction (see THS-PBA-03-US Study Report Appendix 16.1.1).

Table 5 Different Combinations of Evidence Statements and Warnings tested in THS-PBA-03-US

	Claim	Warning
Message 1 **Reduced Exposure**	With the exception of nicotine, with THS 2.2 there is a significant reduction in the production of harmful or potentially harmful chemicals	• **It has not been demonstrated** that switching to THS 2.2 reduces the risk of developing tobacco-related diseases compared to smoking cigarettes. • THS 2.2 tobacco sticks contain nicotine which is addictive. • Using THS 2.2 can harm your health.
Message 2 **Reduced Exposure**	With the exception of nicotine, with THS 2.2 there is a significant reduction in the production of harmful or potentially harmful chemicals	• A significant reduction in the production of harmful chemicals, compared to cigarettes, **does not mean a reduction in the risk of developing tobacco-related diseases.** • THS 2.2 tobacco sticks contain nicotine which is addictive. • Using THS 2.2 can harm your health.
Message 3 **Reduced Exposure**	Scientific studies have shown that switching completely from cigarettes to THS 2.2 significantly reduces your body's exposure to harmful or potentially harmful chemicals.	• **It has not been demonstrated** that switching to THS 2.2 reduces the risk of developing tobacco-related diseases compared to smoking cigarettes. • THS 2.2 tobacco sticks contain nicotine which is addictive. • Using THS 2.2 can harm your health.

(table continues)

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	Claim	Warning
Message 4 **Reduced Exposure**	Scientific studies have shown that switching completely from cigarettes to THS 2.2 significantly reduces your body's exposure to harmful or potentially harmful chemicals.	• A significant reduction in your body's exposure to harmful chemicals, compared to cigarettes, **does not mean a reduction in the risk of developing tobacco-related diseases.** • THS 2.2 tobacco sticks contain nicotine which is addictive. • Using THS 2.2 can harm your health.
Message 5 **Reduced Risk**	Scientific studies have shown that switching completely from cigarettes to THS 2.2 can reduce the risks of tobacco-related diseases.	• Reduced risk **does not mean no risk.** The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use. • THS 2.2 tobacco sticks contain nicotine which is addictive. • Using THS 2.2 can harm your health.

Data Source: Study Report THS-PBA-03-US Appendix 16.1.1.

Results

Comprehension

In the main sample, a majority of subjects answered correctly that "*with THS, exposure to harmful and potentially harmful constituents (HPHCs) is significantly reduced compared to CC"* (70% of subjects for Message 1, 71% for Message 2, 55% for Message 3, 57% for Message 4, and 51% for Message 5; refer to Table 5 for Message numbering). Comprehension on HPHCs reduction was higher for those THS Messages for which the HPHCs graph was included (Message 1 and 2). This suggests that the HPHCs graph helped to facilitate comprehension on HPHC levels. This interpretation was supported by the analysis of open-ended responses which indicated many subjects who correctly answered the comprehension assessment on HPHCs referenced the graph to support their response (49% for Message 1, 39% for Message 2). However, the HPHCs graph was also referenced by some subjects who *incorrectly* answered the comprehension question on HPHCs (19% for Message 1, 17% for Message 2). Therefore, the graph appears to have helped some subjects correctly answer the HPHCs question but also misled some subjects with respect to the information on HPHCs.

The level of comprehension on risk of tobacco-related diseases related to switching from CC to THS was the highest for Messages 3 and 5 (62% of subjects for Message 1, 64% for Message 2, 74% for Message 3, 60% for Message 4, and 81% for Message 5; refer to Table 5 for Message numbering). For Messages 1 to 4, between 18% and 35% of subjects incorrectly responded that "*using THS reduces the risk of tobacco-related diseases*" (32%, 28%, 18% and 35% for Messages 1, 2,3 and 4, respectively). For all THS messages, less than 2% of subjects indicated that THS can "eliminate" the risk of tobacco-related diseases and thus underestimated the health risk of THS.

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The comprehension results in *LA-25 Adult Never Smokers* were similar to those observed in the *Main Sample*. *Specific Comprehension* focused on subjects' comprehension of specific information presented as part of 3 sections of the THS Messages: Intended Users Statement, Evidence Statement, and Warning Statements (Section 6.4.2.1). The levels of Specific Comprehension were consistently high across all the THS messages for the Intended User Section (≥94% across all messages), the Available Evidence to Date Section (>85% across all messages), and the Important Warning Section (>76% across all messages).

Risk Perception

Overall, all 3 domains of risk perception (i.e., Perceived Health Risk, Perceived Addiction Risk, and Perceived Harm to Others) showed a similar pattern of results across the 5 THS messages and the 5 smoking groups (i.e., Adult Smokers with Intention to Quit CC, Adult Smokers with no Intention to Quit CC, Adult Former Smokers, Adult Never Smokers, Adult LA-25 Never Smokers). Regardless of the message subjects were exposed to, subjects rated CC with the highest *Perceived Health Risk*, while they rated NRTs and Cessation with the lowest risk. THS tended to be perceived as the next most risky product. For all messages, and regardless of the smoking groups, E-cigarettes were consistently perceived as being of lower risk than THS, and as being of higher risk than NRTs/Cessation. Overall, the results for *Perceived Addiction Risk* and *Perceived Harm to Others* were broadly consistent with *Perceived Health Risk*: CC was perceived as the most risky product, THS as an intermediate risk product, and NRTs/Cessation as the least risky product.

In terms of consumer understanding and perception, the reduced risk message (Message 5) performed well overall, as it was associated with (i) a high level of comprehension that switching completely from CC to THS can reduce risks of tobacco-related diseases (81% of correct answers) and (ii) a level of risk perception for THS between CC and Cessation/NRTs. The 4 reduced exposure messages (Messages 1 to 4) performed similarly: they were each associated with patterns of risk perception ratings that placed THS between the highest comparator (CC) and the lowest comparator (NRTs/Cessation). However, results also highlighted the challenge of communicating a reduced exposure claim without any subject inferring some degree of reduced risk for disease. Overall, Message 3 performed better than the other reduced exposure messages (Messages 1, 2, and 4) in terms of comprehension of the claim that switching to THS involves no established reduction in disease risk (74% of correct answers). Therefore, the comprehension results provided a basis for selecting Message 3 and Message 5 to be developed further into THS label, labeling and marketing material.

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6.4.3.3 THS-PBA-04-US Study

The main purpose of this qualitative study was to contribute to the development of THS potential label, labeling and marketing material by exploring how each element of the materials contributes to the *Comprehension* of the modified risk information, *Intent to Use* THS, and *Risk Perception* of THS compared to other tobacco and nicotine-containing products, and compared to quitting tobacco use.

Methodology

A brief description of the study methods is provided in Table 6.

Table 6 Methodology of THS-PBA-04-US

Study Title: Qualitative Study to Develop THS 2.2 Potential Label, Labeling and Marketing Material
Study design: 2-cities qualitative study, which consisted of 30 individual interviews (IDIs): 2 pilot IDIs and 28 main study IDIs, designed to capture participants' comments and responses when exposed to specific communication materials.
Subjects: Subjects: Enrolled: 30; Full analysis population (FAP): 28; Number of adult smokers in the FAP: 20; Number of adult former smokers in the FAP: 4; Number of adult never smokers in the FAP: 4.
Main criteria for inclusion: Aged 18 or older Adult Smokers with no Intention to Quit CC: currently smoking at least 1 CC/day, started more than 30 days ago with no intention to quit within 6 months; Adult Smokers with Intention to Quit CC: currently smoking at least 1 CC/day, started more than 30 days ago with the intention to quit within 6 months ; Adult Former Smokers: quit smoking CC more than 30 days ago; Adult Never Smokers Phase 2 only: never smoked or never smoked daily and less than 100 CC
Methods: Moderators (5+ years of experience) were utilized to conduct the IDIs. A discussion guide was employed in each IDI in order to elicit participant feedback in a consistent manner across the various IDIs.
Criteria for Evaluation: Verbal data, transcribed from the IDIs, were examined for each communication material in general and by smoking status in particular to identify the extent of endorsement.

Five potential communication materials were assessed: (i) brochure, (ii) direct mail, (iii) advertising concept, (iv) point of sales advertisement, and (v) (b) (4) In the brochure and direct mail, 3 potential claims selected on the basis of [THS-PBA-02-US] findings were included (Table 7).

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Table 7 Modified Risk Claims assessed in THS-PBA-04-US

Reduced Exposure A	Reduced Exposure B	Reduced Risk
• With the exception of nicotine, with the *iQOS* system there is a significant reduction in the production of harmful or potentially harmful chemicals.	• Scientific studies have shown that switching completely from cigarettes to the *iQOS* system significantly reduces your body's exposure to harmful or potentially harmful chemicals.	• Scientific studies have shown that switching completely from cigarettes to the *iQOS* system can reduce the risks of tobacco-related diseases.
Important Warning A	**Important Warning B**	**Important Warning C**
• It **has not been demonstrated** that switching to the *iQOS* system reduces the risk of developing tobacco-related diseases compared to smoking cigarettes. • HeatSticks™ contain nicotine which is addictive. • Using the *iQOS* system can harm your health.	• A significant reduction in your body's exposure to harmful chemicals, compared to cigarettes, **does not mean a reduction in the risk of developing tobacco-related diseases**. • HeatSticks™ contain nicotine which is addictive. • Using the *iQOS* system can harm your health.	• Reduced risk **does not mean no risk**. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco-use. • HeatSticks™ contain nicotine which is addictive. • Using the *iQOS* system can harm your health.

Data Source: Study Report THS-PBA-04-US Appendix b
iQOS is the commercial name and registered trademark for THS. *HeatSticks* is the commercial name and registered trademark for Tobacco Sticks.

Results[3]

Comprehension

Most adult current, former, and never smokers expressed that the reduced risk information was easy to understand. Their statements indicated that they appreciated the clear and direct message "reduced risk does not mean no risk". After reading the reduced risk claim, subjects commented that there is a health risk associated with using THS; however, that risk was described as being reduced compared to CC.

> *"It's saying that just like every other thing you smoke, just like cigarettes, it's harmful. But it's saying that it's not as harmful as cigarettes and it's saying that just because we're offering a reduced risk system does not mean that you're completely escaping all the harmful possible diseases that you could get along the way."* (Adult smoker, male, 18-25, Phoenix)

> *"Reduced risk does not mean no risk…they are pointing out what's important by going with the bolder print…it just pops it out there, I mean keep it simple stupid…So, there is no misleading. If you want no risk, quit smoking."* (Former smoker, female, 51+, Phoenix)

[3] Verbatims are shown for illustrative purposes.

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Participants described reduced exposure claims A and B (see Table 7) as being clearly written and understandable. At the same time, some subjects' comments suggested there was ambiguity in both claims A and B, citing the available evidence to date (which leads to the expectation that switching to THS may potentially reduce the health risk when compared to CC), and important warning elements of the claims (there is no link between the reduction in the production of, or exposure to, harmful or potentially harmful chemicals and the reduction of the risk of developing tobacco-associated diseases) to be contradictory.

> *"In the Available Evidence to Date it's saying that it could be less harmful because it's not heating up those chemicals that fire would. But then on the Important Warning...it's saying that that's not been proven. It's basically discrediting the information above."* (Adult smoker, male, 18-25, Phoenix)

Risk Perception

Discussion statements made by subjects in each group described THS as having a moderate to high health risk.

> *"Knowing that it's real tobacco and still has nicotine, I'm still going to say high risk."* (Adult smoker, female, 26-35, Chicago)

> *"I would say moderate risk but if there was something between the two (moderate and high) I would go there. It clarifies in there you are still essentially smoking. It's tobacco burning just below the burn point which cuts out a lot of the toxins but you're still getting some of the nicotine, the dirt, the tar. I assume you're still getting some tar, maybe not all of it but I would assume you're still getting some."* (Former smoker, male, 36-50, Chicago)

Participants further described THS as having a lower health risk than CC, a similar or higher health risk than E-cigarettes (since all participants describe THS as an e-cigarette but with actual tobacco), and a higher health risk than NRTs or smoking cessation. This perception was held across all communication materials assessed in the study.

The copylines used in the diverse materials were found to be favorable and strengthed the communication of the product. For instance, by using the copylines "real tobacco" and/or "tobacco heating system", THS was clearly described as a tobacco product and it was clearly conveyed to all smoking groups that there is still a health risk associated with using THS.

> *"The tagline, 'real tobacco, no fire.' The real tobacco part is wonderful, that you're not sacrificing the enjoyment of having a cigarette, but that comes with inherent risks."* (Adult smoker, female, 26-35, Chicago)

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Taken together, the findings of this study [THS-PBA-04-US] were consistent with the results found in [THS-PBA-02-US] and [THS-PBA-03-US]. They indicated that the incorporation of additional textual and graphical elements, shown as part of the materials tested, did not impact the understanding of the information on modified risk nor did they influence the perception of risk associated with THS use.

6.4.3.4 Conclusions across Developmental Studies

The development phase generated consistent findings related to (i) comprehension of the information concerning modified risk claims as well as (ii) perception of the risks of using THS in comparison to other tobacco and nicotine-containing products (CC, E-cigarettes), NRTs and Cessation. Based on these findings, 2 communications were selected for further development into label, labeling and marketing material:

(1) One communication including a reduced risk claim (RRC) and
(2) One communication including a reduced exposure claim (REC)

Table 8 summarizes the results obtained across [THS-PBA-02-US], [THS-PBA-03-US] and [THS-PBA-04-US] studies that support the evidence on appropriate comprehension and risk perception for RRC and REC messages.

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Table 8 Summary of the Performance of RRC and REC Messages through the Development Phase

Measure	Claim	THS-PBA-02-US	THS-PBA-03-US	THS-PBA-04-US
Comprehension	RRC	Message J (Table 3) perceived as clear, broadly relevant, easy to understand, honest, straight forward, and credible (e.g., reference to scientific data).	High comprehension level that switching completely from CC to THS can reduce risks of tobacco-related diseases .	Claim C (Table 7) perceived as easy to understand.
	REC	Message C (Table 3) perceived as clear, broadly relevant, easy to understand, honest, straight forward, and credible (e.g., reference to scientific data).	Comprehension level of no reduction of tobacco-related diseases higher for Message 3 compared to other "reduced exposure" messages (Messages 1, 2 and 4).	Claim B (Table 7) clearly written and understandable. At the same time, the available evidence to date and important warning elements of claim B are perceived by the subjects as contradictory.
Risk Perception	RRC	Evidence that THS is perceived as less risky than CC (the highest risk comparator) but more risky than NRTs and quitting smoking (the lowest risk comparators). Evidence also that THS is considered at higher risk than e-cigarettes.		
	REC	Evidence that THS is perceived as less risky than CC (the highest risk comparator) but more risky than NRTs and quitting smoking (the lowest risk comparators). Evidence also that THS is considered at higher risk than e-cigarettes. However, results also highlight the challenge of communicating a "reduced exposure" claim without people inferring some degree of reduced risk for disease.		

Abbreviations: RRC = reduced risk claim; REC = reduced exposure claim.

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6.4.4 Assessment Phase

Based on the insights generated during the development phase, 3 types of communications were crafted for the assessment phase:

(1) A communication including Claim #1: "Reduced risks of tobacco-related diseases" based on Message 5 from study [THS-PBA-03-US] (Figure 1)
(2) A communication including Claim #2: "Reduced risk of harm" (Figure 2)
(3) A communication including Claim #3: "Reduced body's exposure to harmful and potentially harmful chemicals" based on Message 3 from study [THS-PBA-03-US] (Figure 3)

AVAILABLE EVIDENCE TO DATE:

- The *iQOS* system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from conventional cigarettes to the *iQOS* system can reduce the risks of tobacco-related diseases.

IMPORTANT WARNING:

- Reduced risk does not mean no risk**.** The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use.
- HeatSticks™ contain nicotine, which is addictive.
- Using the *iQOS* system can harm your health.

Figure 1 Reduced Risk Claim (RRC) and associated Warning

AVAILABLE EVIDENCE TO DATE:

- Switching completely to *iQOS* presents less risk of harm than continuing to smoke cigarettes.

IMPORTANT WARNING:

- Less risk of harm does not mean no risk of harm. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use.
- HeatSticks™ contain nicotine, which is addictive.

Figure 2 Reduced Risk Claim 2 (RRC2) and associated Warning

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AVAILABLE EVIDENCE TO DATE:

- The *iQOS* system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from conventional cigarettes to the *iQOS* system significantly reduces your body's exposure to harmful or potentially harmful chemicals.

IMPORTANT WARNING:

- It has not been demonstrated that switching to the *iQOS* system reduces the risk of developing tobacco-related diseases compared to smoking conventional cigarettes.
- HeatSticks™ contain nicotine, which is addictive.
- Using the *iQOS* system can harm your health.

Figure 3 Reduced Exposure Claim (REC) and associated Warning

The objective of the assessment phase was to describe responses to different instances of label, labeling and marketing material in the following populations: Adult Smokers with no Intention to Quit CC, Adult Smokers with the Intention to Quit CC, Adult Former Smokers, and Adult Never Smokers. Furthermore, the assessment phase was aiming at providing evidence that THS labeling and advertising as proposed in this application:

(1) Will allow the public to fully understand the information concerning modified risk
(2) Will effectively communicate the risks associated with THS
(3) Will lead adult former, never, and current smokers with intention to quit to clearly understand that THS is not intended for them

The assessment phase included 3 studies, [THS-PBA-05-RRC-US], [THS-PBA-05-RRC2-US], [THS-PBA-05-REC-US], all using a similar methodology and a randomized parallel 5-arm design, with subjects in each arm being presented with an instance of THS communication material (Table 9).

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Table 9 THS Communication Materials, Warning Type and Study Arms

		Type of Communication Material		
		THS Brochure	**Tobacco Sticks Pack**	**THS Direct Mail**
Warning Type	**Surgeon General**[a]	Arm 1	Arm 3	NA
	PMI[b]	Arm 2	Arm 4	Arm 5

Abbreviations: NA = not assessed; THS = Tobacco Heating System.
[a] The Surgeon General (SG) warnings currently mandated for CC include: 1) "Smoking causes lung cancer, heart disease, emphysema, and may complicate pregnancy."; 2) "Quitting smoking now greatly reduces serious risks to your health." ; 3) "Smoking by pregnant women may result in fetal injury, premature birth, and low birth weight."; 4) "Cigarette smoke contains carbon monoxide." Note: Subjects randomized to the Surgeon General's warning were assigned 1 of the 4 warnings randomly.
[b] The PMI Important Warning statements were adapted for each study to present a coherent set of information between the claim and the warning concerning modified risk (see Figure 1, Figure 2, and Figure 3 for RRC, RRC2 and REC, respectively).

Considering 2 warning types was to assess how *Comprehension, Risk Perception and Intent to Use* were related to both the currently mandated Surgeon General warnings for CC and the Important Warning developed by PMI.

The section below reports only the major results related to *Comprehension* and *Risk Perception* of [THS-PBA-05-RRC-US], [THS-PBA-05-RRC2-US] and [THS-PBA-05-REC-US] studies. More details can be found in the summary or full report of the individual studies presented in the Section 7.3.2.

6.4.4.1 THS-PBA-05-RRC-US Study

Methodology

A brief description of the study methods is provided in Table 10.

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Table 10 Methodology of THS-PBA-05-RRC-US

Study Title: Quantitative Assessment of THS 2.2 Label, Labeling, and Marketing Material with Reduced Risk Claims

Study Design: 4 cities, 5-arm parallel-group experiment. The 5 arms corresponded to 5 different combinations of communication materials and warning type, each of the materials being tested by approximately equal numbers of subjects from different smoking status groups.

Subjects: *Full Sample* (N=2255) stratified into Adult Smokers with no Intention to Quit CC (N=472), Adult Smokers with the Intention to Quit CC (N=472), Adult Former Smokers (N=471) and Adult Never Smokers (N=477). An additional oversampling of 478 Adult Never Smokers from the legal age of smoking to 25 years of age (*LA-25 Adult Never Smokers*) which includes 115 Adult Never Smokers from the *Main Sample*.

Main Criteria for Inclusion:

Aged 18 and above, or above state legal smoking age if above 18 years

Adult Smokers with no Intention to Quit CC[a]: currently smoking some days or every day, started more than 30 days ago with no intention to quit within 6 months; Adult Smokers with Intention to Quit CC[a]: currently smoking some days or every day, started more than 30 days ago with the intention to quit within 6 months; Adult Former Smokers: quit smoking CCs more than 30 days ago; Adult Never Smokers: never smoked or never smoked daily and less than 100 CC

Methods:

Comprehension

Closed questions on Global and Specific Comprehension of THS communication materials [THS-PBA-05-RRC-US Study Report Appendix 16.1.1].

Risk Perception

The PRI-Personal Risk (PRI-P) [A732 PBA01sum] composed of 3 domains:

Perceived Health Risk measured by an 18-item scale

Perceived Addiction Risk measured by a 7-item scale

Perceived Harm to Others measured by 2 single items

Criteria for Evaluation:

Level of Comprehension:

Proportion of subjects correctly answering Comprehension questions, by study arm, for the Main Sample and LA-25 Never Smoker Sample

Risk Perception:

Perceived Health Risk, Perceived Addiction Risk and Perceived Harm to Others for THS and each comparator (i.e., CC, E-cigarettes, NRTs[b] and Cessation[b]), by study arm, and by smoking status group

[a] Include Regular Smokers (smoke at least 1 CC a day) and Intermittent Smokers (between 4 and 27 days per month, with no restrictions on total number of CC smoked over that period, between 10% and 40%).
[b] Not assessed by Adult Never Smokers

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Mockup of THS Brochure, Tobacco Sticks Pack and Direct Mail were presented branded (*iQOS* for THS and *Marlboro* for the Tobacco Sticks) to the subjects with a hypothetical price for the THS device (b) (4) and for a pack of 20 Tobacco Sticks (price of a *Marlboro* pack of CC in the specific city of the research). All materials included at least the following 2 elements:

(1) Information on THS, including the modified risk claim that "*Scientific studies have shown that switching completely from conventional cigarettes to the iQOS system can reduce the risks of tobacco-related diseases*".
(2) Warning Section (Surgeon General's warnings or PMI Important Warning)

The mockups are presented in [THS-PBA-05-RRC-US Study Report Appendix 16.1.1].

Results

Comprehension

The majority of subjects answered correctly that "*the risk of tobacco-related diseases can be reduced by completely switching from CC to THS"* across all study arms (THS Brochure: 63 and 69% of correct answers for Arm 1 and Arm 2, respectively; Tobacco Sticks Pack: 74% and 78% of correct answers for Arm 3 and Arm 4, respectively; Direct Mail: 64% of correct answers; Table 11). With the exception of the Brochure with PMI Important Warning (Arm 2), levels of comprehension of the risk reduction information was higher when presented on the Tobacco Sticks pack than when presented in the Brochure or the Direct Mail. The levels of correct comprehension that "*Exposure to HPHCs is significantly reduced"* was between 49% and 63% across study arms (Table 11). With the exception of the THS Brochure with Surgeon General's warnings (Arm 1), comprehension levels of the exposure reduction information was consistently lower than comprehension levels of the risk reduction information within each study arm (Table 11).

Levels of correct comprehension of specific sections of the THS communication materials was high across materials and warning types (Available Evidence to Date Section: > 95%; Important Warning Section: ≥ 83%; Intended User Section: ≥92%; Table 11). Overall, levels of comprehension were similar in *LA-25 Adult Never Smokers* and the *Main Sample* (THS-PBA-05-RRC-US Study Report Table 15.2.2.2.2).

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Table 11 Main Sample in THS-PBA-05-RRC-US: Proportion of Subjects with Correct Global and Specific Comprehension by Material and by Warning Type

THS Communication Material	THS Brochure		Tobacco Sticks Pack		THS Direct Mail
Arm	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Warning	SG	PMI	SG	PMI	PMI
Correct Answer	% (n) (95% CI)	% (n) (95% CI)	% (n) (95% CI)	% (n) (95% CI)	% (n) (95% CI)
Global Comprehension					
The risk of tobacco-related diseases can be reduced by completely switching from CC to *iQOS*	62.5 (235) (57.4, 67.4)	69.1 (262) (64.2, 73.7)	74.4 (279) (69.7, 78.7)	77.8(295) (73.3, 81.9)	63.8(243) (58.7, 68.6)
Exposure to HPHCs is significantly reduced	61.7 (232) (56.6, 66.6)	54.4 (206) (49.2, 59.4)	61.9 (232) (56.7, 66.8)	63.3 (240) (58.3, 68.2)	49.1 (187) (44.0, 54.2)
Specific Comprehension					
Evidence Section *iQOS* heats tobacco but does not burn it	96.8 (364) (94.5, 98.3)	97.9 (371) (95.9, 99.1)	96.3 (361) (93.8, 97.9)	96.3 (365) (93.9, 98.0)	95.8 (365) (93.3, 97.6)
Warning Section *iQOS* contains nicotine, which is addictive	NA	88.4 (335) (84.7, 91.4)	NA	90.0 (341) (86.5, 92.8)	86.6 (330) (82.8, 89.9)
The best way to reduce the risk of tobacco-related diseases is to completely quit tobacco use	NA	87.9 (333) (84.1, 91.0)	NA	83.1 (315) (79.0, 86.7)	90.0 (343) (86.6, 92.8)
iQOS can harm your health	NA	85.0 (322) (81.0, 88.4)	NA	86.3 (327) (82.4, 89.6)	86.1 (328) (82.2, 89.4)
Intender Users Section *iQOS* is for smokers who want to continue using tobacco	92.3 (347) (89.1, 94.8)	93.4 (354) (90.4, 95.7)	NA	NA	NA

Abbreviations: CI = confidence interval; HPHCs = harmful and potentially harmful constituents; NA = not applicable; SG = Surgeon General. *iQOS* is the commercial name and registered trademark for THS.
Data Source: Study Report THS-PBA-05-RRC-US, Table 15.2.2.2.1.

Risk Perception

Positioning of THS and comparators CC, E-cigarettes, NRTs and Cessation on the 2 Perceived Risk scales (Health and Addiction) was broadly consistent across the 3 THS communication materials and the 2 warning types (see Figure 4 and Figure 5 for THS Brochure; Figure 6 and Figure 7 for Tobacco Sticks Pack; and THS-PBA-05-RRC-US Study Report Figure 15.1.3.1.5 and Figure 15.1.3.2.5 for THS Direct Mail).

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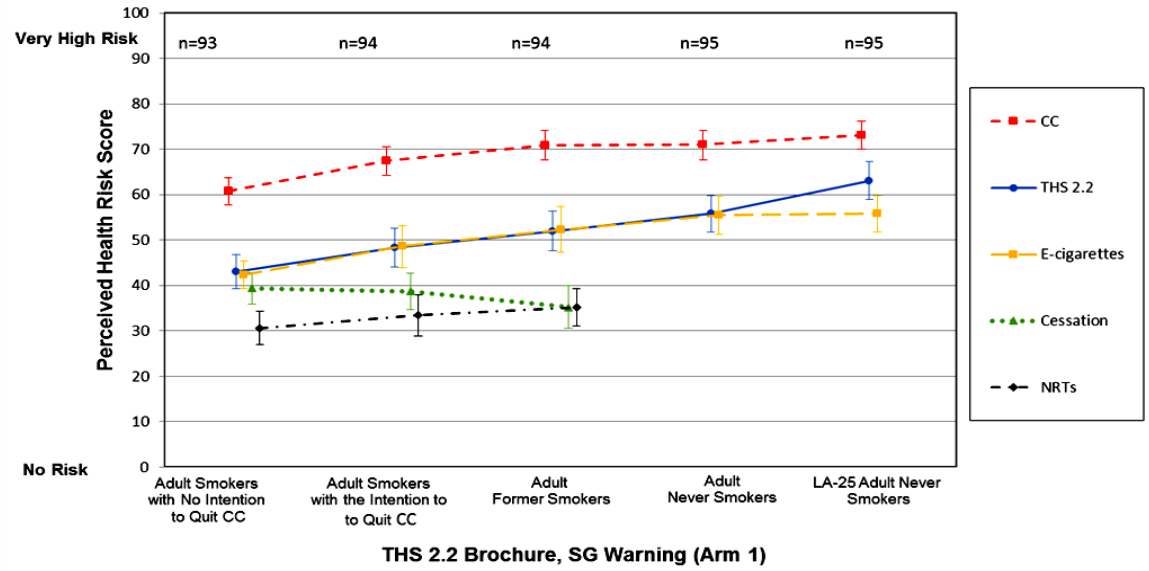
Across all smoking status groups, CC was consistently rated as having the highest *Perceived Health Risk*. For Adult Smokers with no Intention to Quit CC, Adult Smokers with the Intention to Quit CC, and Adult Former Smokers, THS was consistently rated with an "intermediate" *Perceived Health Risk*, in that it was associated with mean Perceived Health Risk ratings below CC and above the lowest Perceived Health Risk comparators (either NRTs or Cessation). Across all smoking status groups, THS was rated as having mean *Perceived Health Risk* ratings similar to E-cigarettes. Adult Smokers with no Intention to Quit CC and Adult Smokers with the Intention to Quit CC, rated the *Perceived Addiction Risk* of THS between the highest risk comparator (consistently CC) and the lowest comparator (NRTs or Cessation). In contrast to *Perceived Health Risk*, THS was positioned on the *Perceived Addiction Risk* scale closer to CC for Adult Former Smokers and Adult Never Smokers compared to Adult Smokers (both with and with no Intention to Quit CC).

As for Comprehension assessment, perceived risk ratings were similar for LA-25 Adult Never Smokers and Adult Never Smokers from the Main Sample (see THS-PBA-05-RRC-US Study Report Table 15.2.2.3.1, Table 15.2.2.3.2 and Table 15.2.2.3.3).

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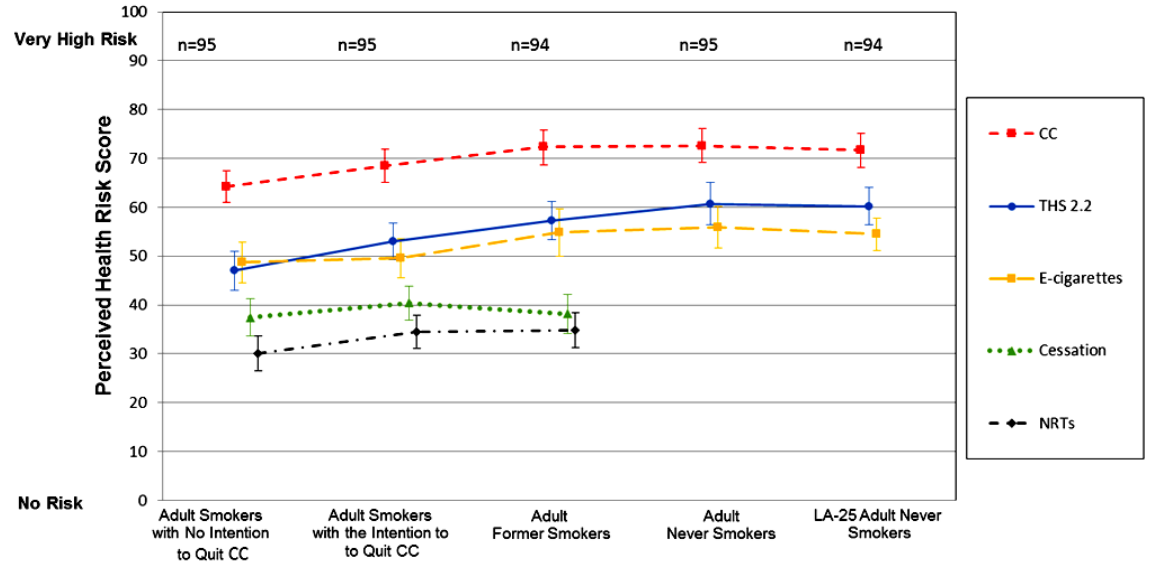
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A



THS 2.2 Brochure, SG Warning (Arm 1)

B



THS 2.2 Brochure, PMI Warning (Arm 2)

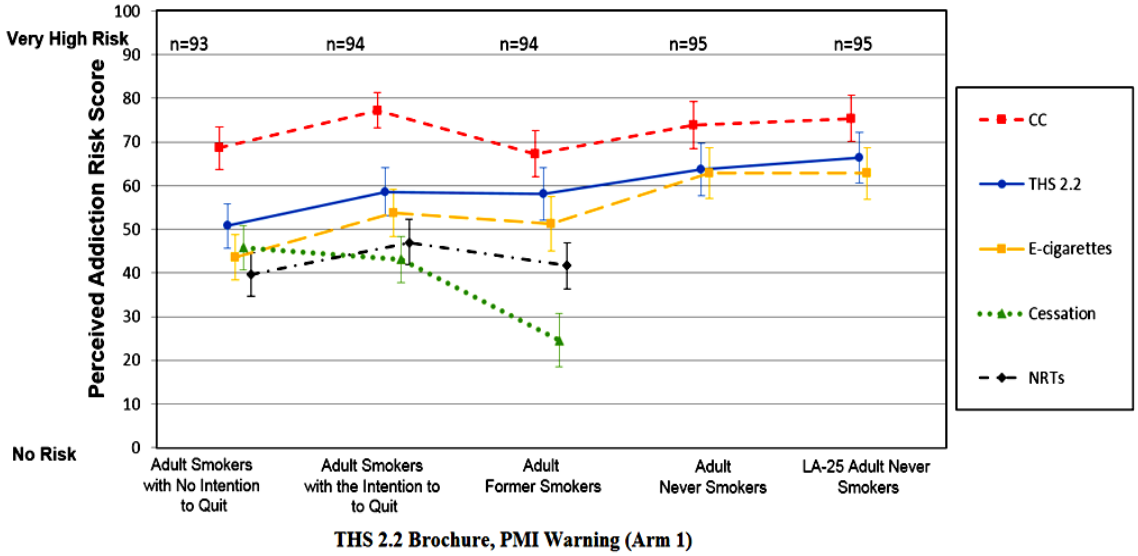
Abbreviations: CC = conventional cigarette; LA = legal age; NRT = nicotine replacement therapy; THS = Tobacco Heating System.
Error bars are the 95% confidence intervals of the mean.
Note: Adult Never Smokers group includes only those Adult Never Smokers from the Main Sample.
Note: connecting lines are only to highlight clustering of outcomes for each comparator along the y-axis.
Data Source: Study Report THS-PBA-05-RRC-US, Figure 15.1.3.1.1 and Figure 15.1.3.1.2.

Figure 4 Perceived Health Risk – THS Brochure with Surgeon General's Warnings: Arm 1 (A) and with PMI Warning: Arm 2 (B) in THS-PBA-05-RRC-US

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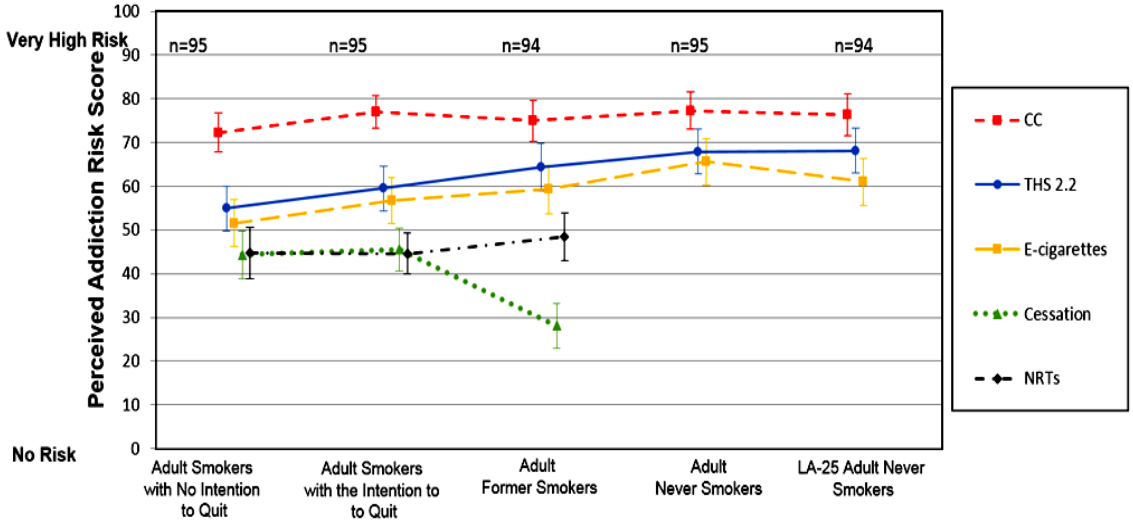
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A



THS 2.2 Brochure, PMI Warning (Arm 1)

B



THS 2.2 Brochure, PMI Warning (Arm 2)

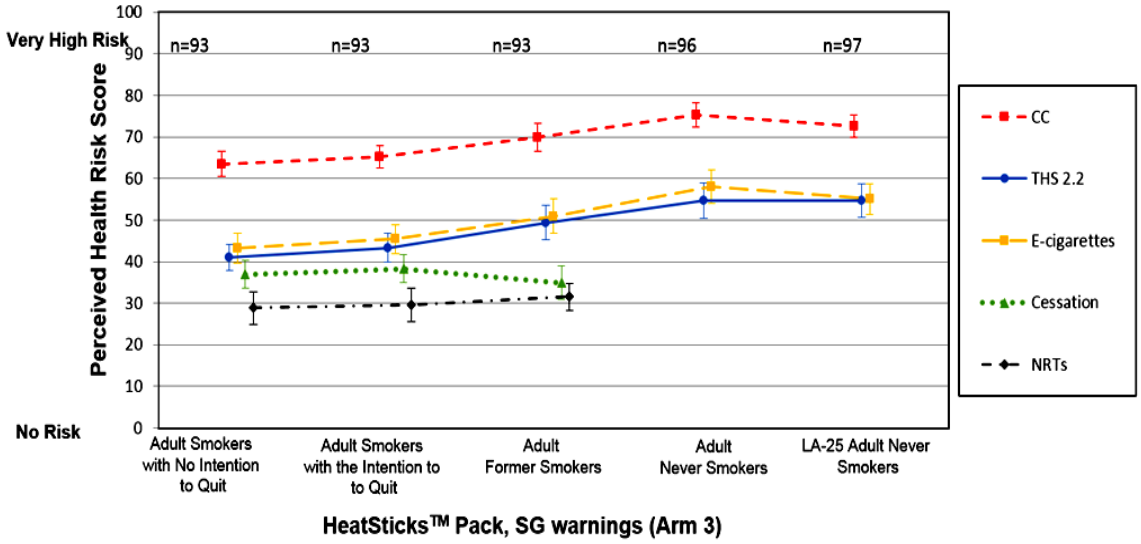
Abbreviations: CC = conventional cigarette; LA = legal age; NRT = nicotine replacement therapy; THS = Tobacco Heating System.
Error bars are the 95% confidence intervals of the mean.
Note: Adult Never Smokers group includes only those Adult Never Smokers from the Main Sample.
Note: connecting lines are only to highlight clustering of outcomes for each comparator along the y-axis.
Data Source: Study Report THS-PBA-05-RRC-US, Figure 15.1.3.2.1 and Figure 15.1.3.2.2.

Figure 5 Perceived Addiction Risk – THS Brochure with Surgeon General's Warnings: Arm 1 (A) and with PMI Warning: Arm 2 (B) in THS-PBA-05-RRC-US

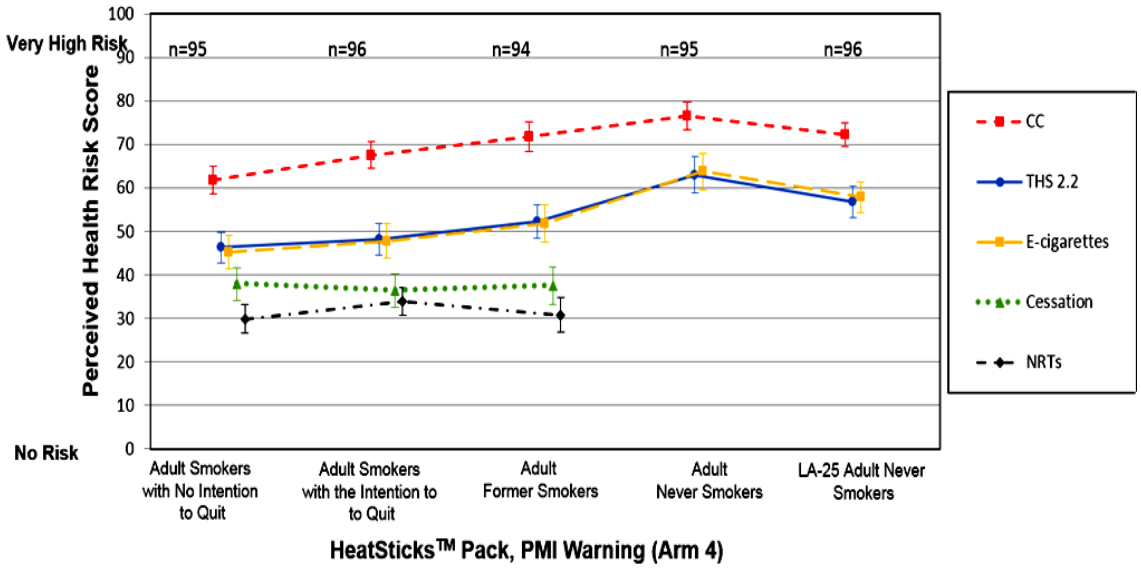
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A



B



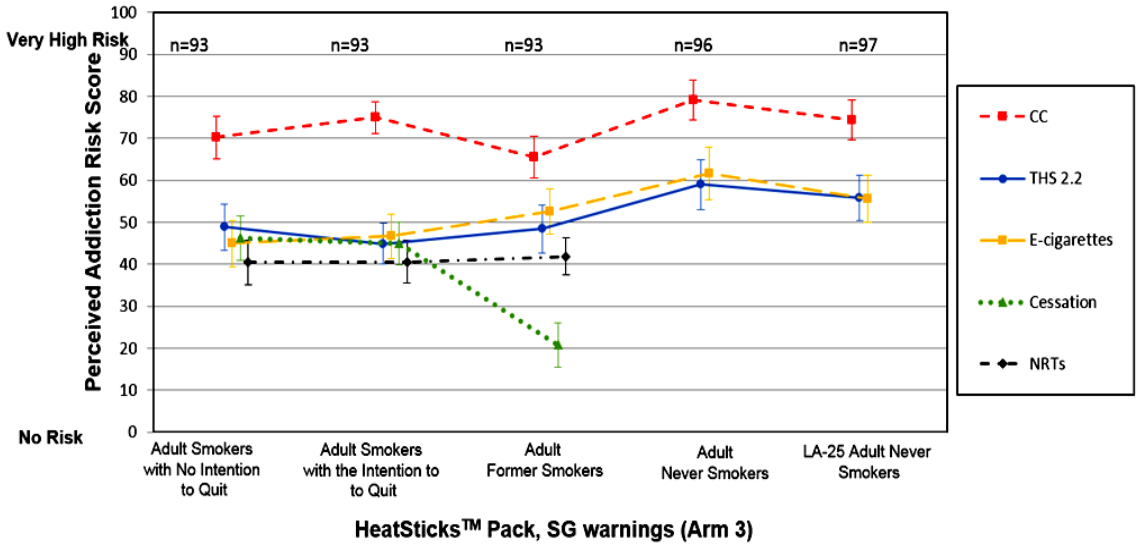
Abbreviations: CC = conventional cigarette; LA = legal age; NRT = nicotine replacement therapy; THS = Tobacco Heating System.
Error bars are the 95% confidence intervals of the mean.
Note: Adult Never Smokers group includes only those Adult Never Smokers from the Main Sample.
Note: connecting lines are only to highlight clustering of outcomes for each comparator along the y-axis.
Data Source: Study Report THS-PBA-05-RRC-US, Figure 15.1.3.1.3 and Figure 15.1.3.1.4.

Figure 6 Perceived Health Risk – Tobacco Sticks Pack with Surgeon General's Warnings: Arm 3 (A) and with PMI Warning: Arm 4 (B) in THS-PBA-05-RRC-US

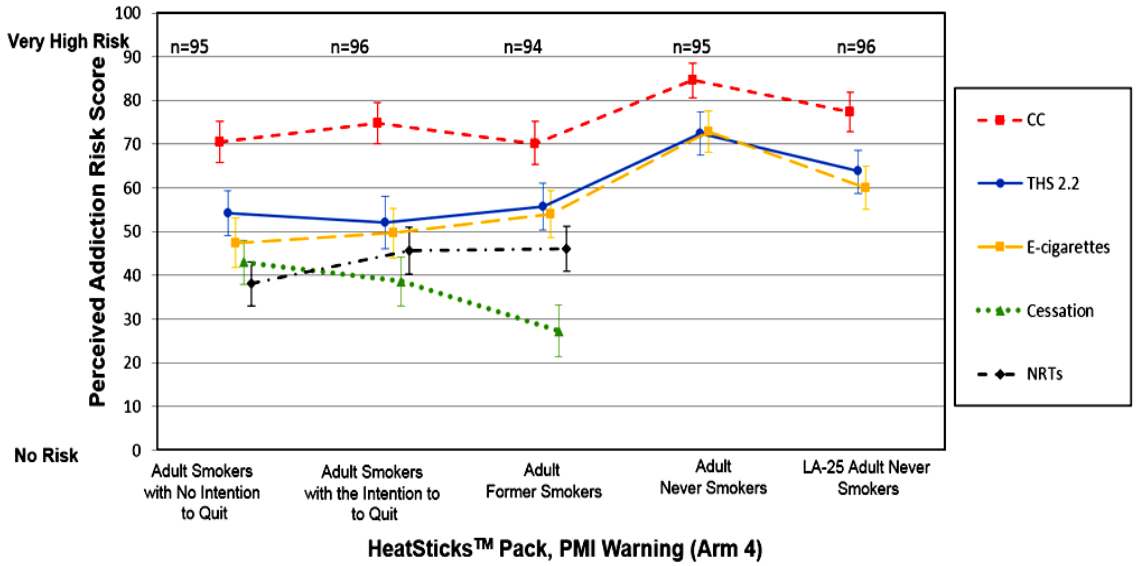
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A



B



Abbreviations: CC = conventional cigarette; LA = legal age; NRT = nicotine replacement therapy; THS = Tobacco Heating System.
Error bars are the 95% confidence intervals of the mean.
Note: Adult Never Smokers group includes only those Adult Never Smokers from the Main Sample.
Note: connecting lines are only to highlight clustering of outcomes for each comparator along the y-axis.
Data Source: Study report THS-PBA-05-RRC-US, Figure 15.1.3.2.3 and Figure 15.1.3.2.4.

Figure 7 Perceived Addiction Risk – Tobacco Sticks Pack with Surgeon General's Warnings: Arm 3 (A) and with PMI Warning: Arm 4 (B) in THS-PBA-05-RRC-US

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6.4.4.2 THS-PBA-05-RRC2-US Study

Methodology

A brief description of the Study methods is provided in Table 12.

Table 12 Methodology of THS-PBA-05-RRC2-US

Study Title: Second Quantitative Assessment of THS Label, Labeling and Marketing Material with Reduced Risk Claims
Study Design: 4-cities, 5-arm parallel-group experiment. The 5 arms corresponded to 5 different combinations of communication materials and warning type, each of the materials being tested by approximately equal numbers of subjects from different smoking status groups.
Subjects: *Full Sample* (N=2247) stratified into Adult Smokers with no Intention to Quit CC (N=471), Adult Smokers with the Intention to Quit CC (N=475), Adult Former Smokers (N=469) and Adult Never Smokers (N=468). An additional oversampling of 471 Adult Never Smokers from the legal age of smoking to 25 years of age (*LA-25 Adult Never Smokers*) which includes 107 Adult Never Smokers from the *Main Sample*.
Main Criteria for Inclusion: • Aged 18 and above, or above state legal smoking age if above 18 years • Adult Smokers with no Intention to Quit CC[a]: currently smoking some days or every day, started more than 30 days ago with no intention to quit within 6 months; Adult Smokers with Intention to Quit CC[a]: currently smoking some days or every day, started more than 30 days ago with the intention to quit within 6 months; Adult Former Smokers: quit smoking CCs more than 30 days ago; Adult Never Smokers: never smoked or never smoked daily and less than 100 CC
Methods: Comprehension Closed questions on Global and Specific comprehension of THS communication materials [THS-PBA-05-RRC2-US Study Report Appendix 16.1.1] Risk Perception The PRI-Personal Risk (PRI-P) [A732 PBA01sum] composed of 3 domains: • Perceived Health Risk measured by an 18-item scale • Perceived Addiction Risk measured by a 7-item scale • Perceived Harm to Others measured by 2 single items
Criteria for Evaluation: Level of Comprehension: Proportion of subjects correctly answering Comprehension questions, by study arm, for the Main Sample and LA-25 Never Smoker Sample Risk Perception: Perceived Health Risk, Perceived Addiction Risk and Perceived Harm to Others for THS and each comparator (i.e., CC, E-cigarettes, NRTs[b] and Cessation[b]), by study arm and smoking status group

[a] Include Regular Smokers (smoke at least 1 CC a day) and Intermittent Smokers (between 4 and 27 days per month, with no restrictions on total number of CC smoked over that period, between 10% and 40%).
[b] Not assessed by Adult Never Smokers

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Mockup of THS Brochure, Tobacco Sticks Pack and Direct Mail were presented branded (*iQOS* for THS and *Marlboro* for the Tobacco Sticks) to the subjects with a hypothetical price for the THS device (b) (4) and for a pack of 20 Tobacco Sticks (price of a *Marlboro* pack of CC in the specific city of the research). All materials included at least the following 2 elements:

(1) Information on THS, including the modified risk claim that "*Switching completely to iQOS presents less risk of harm than continuing to smoke cigarettes*".
(2) Warning Section (Surgeon General's warnings or PMI Important Warning)

The mockups are presented in [THS-PBA-05-RRC2-US Study Report Appendix 16.1.1].

Results

Comprehension

Levels of correct comprehension that *Switching completely from CC to THS presents less risk of harm* ranged between 56% and 78% across all study arms (Table 13). Levels of correct comprehension of specific sections were high across all materials and warning types (Available Evidence to Date Section: >95%; Important Warning Section: >87%; Intended User Section: >92%; Table 13). Overall, level of comprehension was similar for *LA-25 Adult Never Smokers* and the *Main Sample* (see THS-PBA-05-RRC2-US Study Report Table 15.2.2.2.2).

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Table 13 Main Sample in THS-PBA-05-RRC2-US: Proportion of Subjects with Correct Global and Specific Comprehension by Material and by Warning Type

THS Communication Material	THS Brochure		Tobacco Sticks Pack		THS Direct Mail
Arm	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Warning	SG	PMI	SG	PMI	PMI
Correct Answer	% (n) (95% CI)	% (n) (95% CI)	% (n) (95% CI)	% (n) (95% CI)	% (n) (95% CI)
Global Comprehension					
Switching from CC to *iQOS* presents less risk of harm	56.1 (212) (50.9, 61.2)	73.5 (275) (68.7, 77.9)	72.8 (273) (68.0, 77.2)	78.4 (298) (73.9, 82.5)	77.2 (288) (72.6, 81.4)
Specific Comprehension					
Evidence Section					
iQOS heats tobacco but does not burn it	97.9 (370) (95.9, 99.1)	95.7 (358) (93.1, 97.5)	NA	NA	94.9 (354) (92.2, 96.9)
Warning Section					
iQOS contains nicotine, which is addictive	NA	91.7 (343) (88.4, 94.3)	NA	87.6 (333) (83.9, 90.8)	91.4 (341) (88.1, 94.1)
The best way to reduce the risk of tobacco-related diseases is to completely quit tobacco use	NA	90.9 (340) (87.5, 93.6)	NA	88.9 (338) (85.4, 91.9)	90.1 (336) (86.6, 92.9)
Intender Users Section					
iQOS is for smokers who want to continue using tobacco	95.2 (360) (92.6, 97.2)	92.8 (347) (89.7, 95.2)	NA	NA	NA

Abbreviations: CI = confidence interval; NA = not applicable; SG = Surgeon General. *iQOS* is the commercial name and registered trademark for THS
Data Source: Study report THS-PBA-05-RRC2-US, Table 15.2.2.2.1.

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Risk Perception

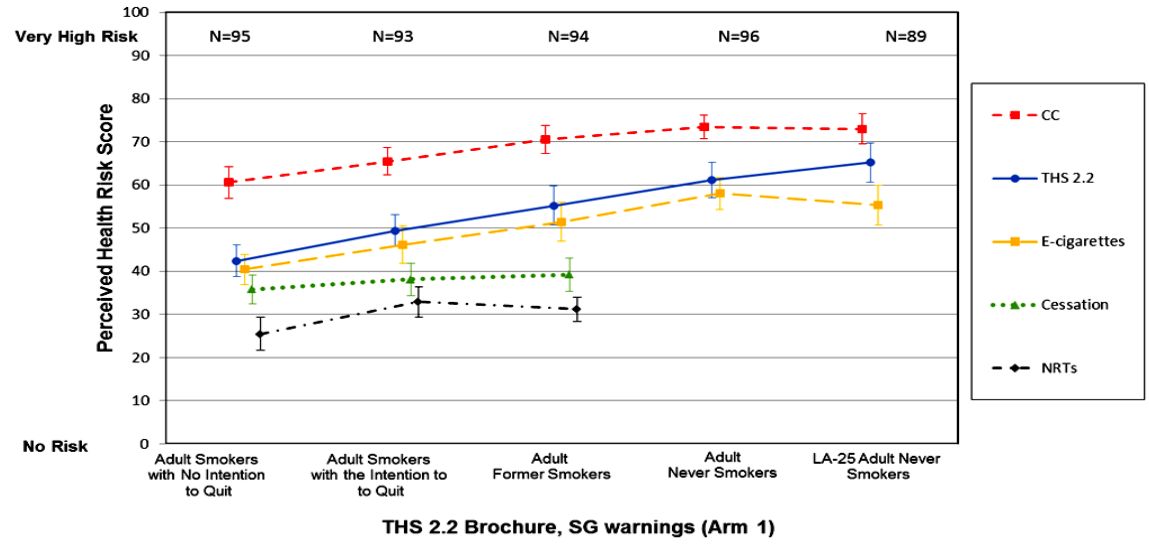
Positioning of THS and comparators CC, E-cigarettes, NRTs and Cessation on the 2 Perceived Risk scales (Health and Addiction) was broadly consistent across the 3 THS communication materials and the 2 warning types (see Figure 8 and Figure 9 for THS Brochure; Figure 10 and Figure 11 for Tobacco Sticks Pack; and THS-PBA-05-RRC2-US Study Report Figure 15.1.3.1.5 and Figure 15.1.3.2.5 for THS Direct Mail). Within all smoking status groups, CC was consistently rated as having the highest *Perceived Health Risk*. For Adult Smokers with no Intention to Quit CC, Adult Smokers with the Intention to Quit CC, and Adult Former Smokers, THS was consistently rated with an "intermediate" Perceived Health Risk, in that it was rated below CC and above the lowest *Perceived Health Risk* comparators (either NRTs or Cessation). Within all smoking status groups, THS was rated as having mean *Perceived Health Risk* ratings similar to E-cigarettes. Adult Smokers with no Intention to Quit CC and Adult Smokers with the Intention to Quit CC rated the *Perceived Addiction Risk* of THS between the highest risk comparator (consistently CC) and the lowest comparator (NRTs or Cessation). In contrast to *Perceived Health Risk*, THS was positioned on the *Perceived Addiction Risk* scale closer to CC for Adult Former Smokers and Adult Never Smokers compared to Adult Smokers (both with and with no Intention to Quit CC).

As for Comprehension assessment, perceived risk ratings were similar *for LA-25 Adult Never Smokers* and Adult Never Smokers from the *Main Sample* (THS-PBA-05-RRC2-US Study Report Tables 15.2.2.3.1, 15.2.2.3.2, and 15.2.2.3.3).

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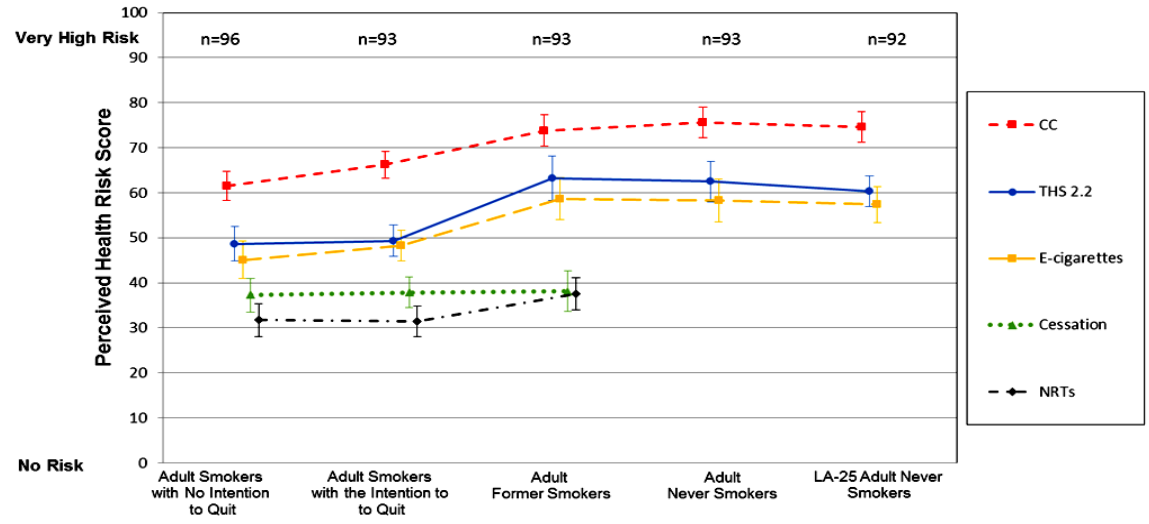
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A



THS 2.2 Brochure, SG warnings (Arm 1)

B



THS 2.2 Brochure, PMI Warning (Arm 2)

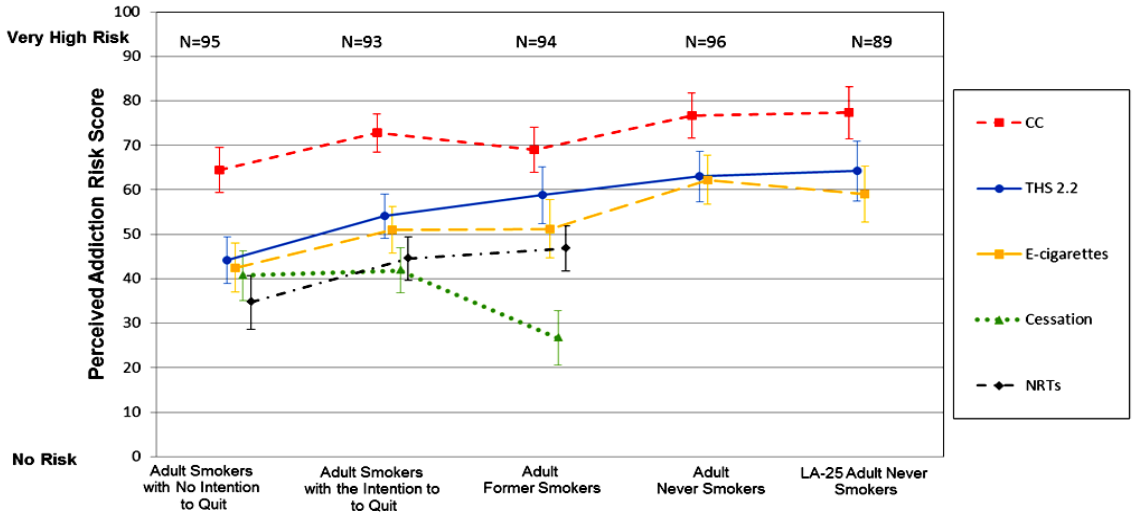
Abbreviations: CC = conventional cigarette; LA = legal age; NRT = nicotine replacement therapy; THS = Tobacco Heating System.
Error bars are the 95% confidence intervals of the mean.
Note: Adult Never Smokers group includes only those Adult Never Smokers from the Main Sample.
Note: connecting lines are only to highlight clustering of outcomes for each comparator along the y-axis.
Data Source: Study report THS-PBA-05-RRC2-US, Figure 15.1.3.1.1 and Figure 15.1.3.1.2.

Figure 8 Perceived Health Risk – THS Brochure with Surgeon General's Warnings: Arm 1 (A) and with PMI Warning: Arm 2 (B) in THS-PBA-05-RRC2-US

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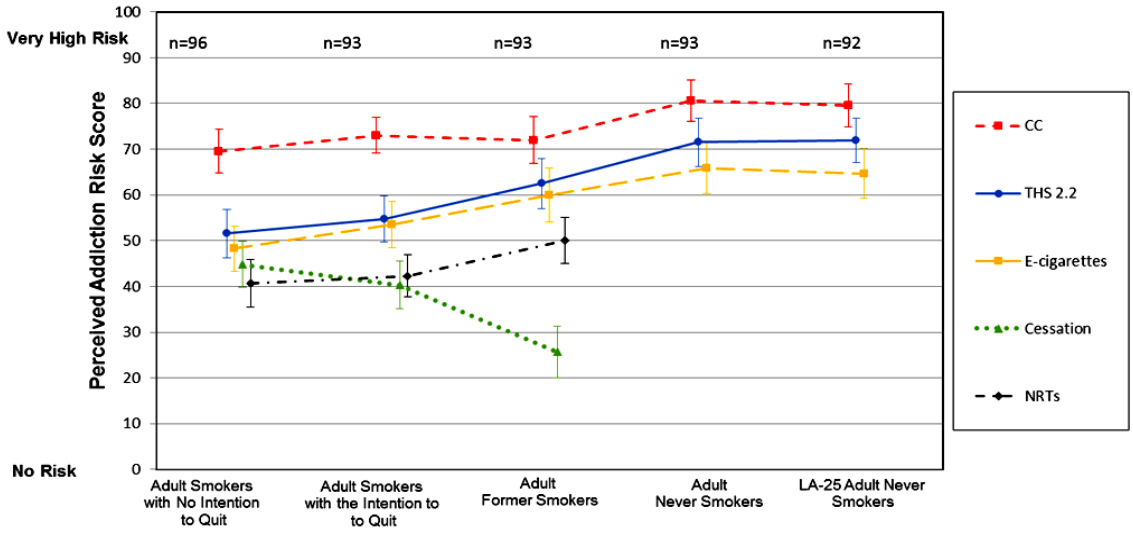
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A



THS 2.2 Brochure, SG warnings (Arm 1)

B



THS 2.2 Brochure, PMI Warning (Arm 2)

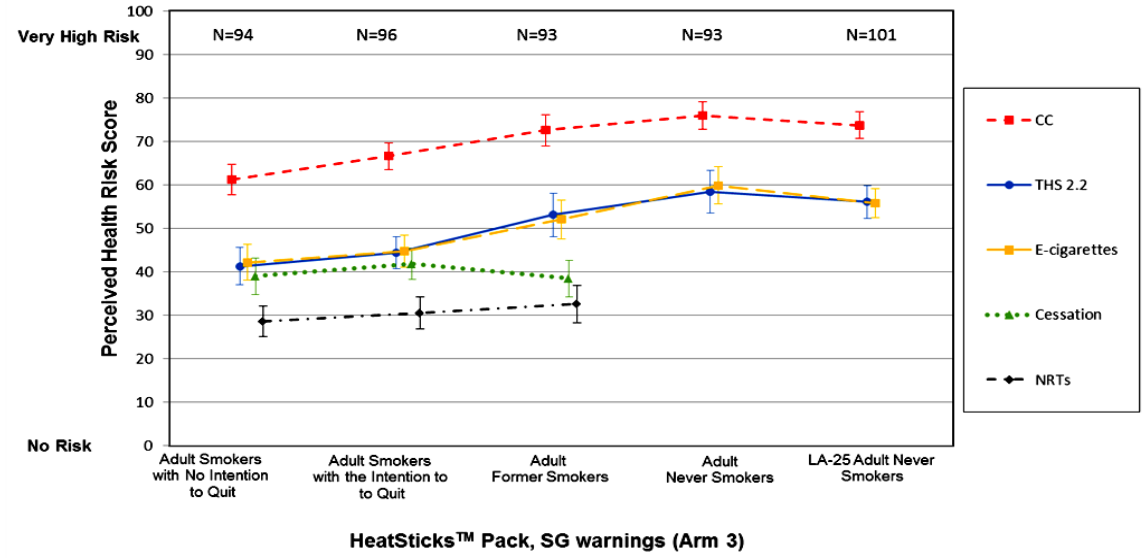
Abbreviations: CC = conventional cigarette; LA = legal age; NRT = nicotine replacement therapy; THS = Tobacco Heating System.
Error bars are the 95% confidence intervals of the mean.
Note: Adult Never Smokers group includes only those Adult Never Smokers from the Main Sample.
Note: connecting lines are only to highlight clustering of outcomes for each comparator along the y-axis.
Data Source: Study Report THS-PBA-05-RRC2-US, Figure 15.1.3.2.1 and Figure 15.1.3.2.2.

Figure 9 Perceived Addiction Risk – THS Brochure with Surgeon General's Warnings: Arm 1 (A) and with PMI Warning: Arm 2 (B) in THS-PBA-05-RRC2-US

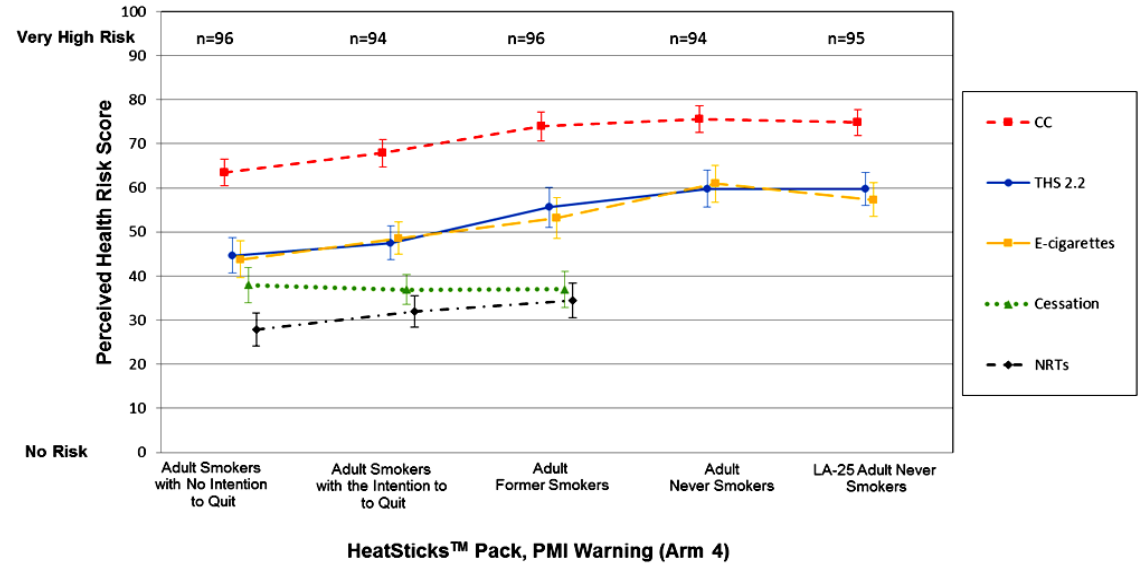
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A



B



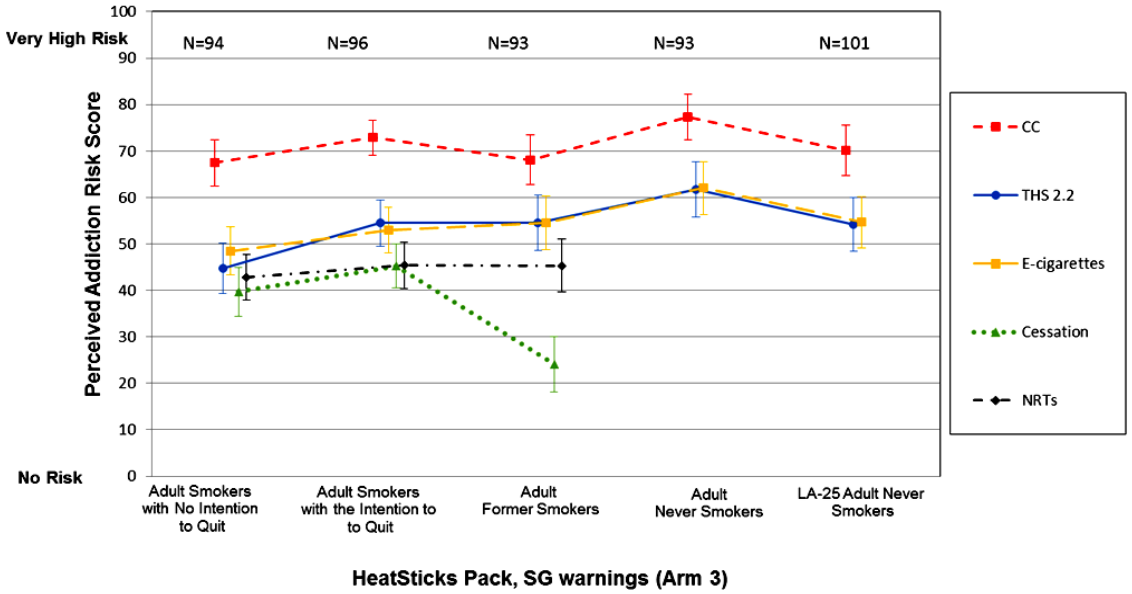
Abbreviations: CC = conventional cigarette; LA = legal age; NRT = nicotine replacement therapy; THS = Tobacco Heating System.
Error bars are the 95% confidence intervals of the mean.
Note: Adult Never Smokers group includes only those Adult Never Smokers from the Main Sample.
Note: connecting lines are only to highlight clustering of outcomes for each comparator along the y-axis.
Data Source: Study Report, THS-PBA-05-RRC2-US, Figure 15.1.3.1.3 and Figure 15.1.3.1.4.

Figure 10 Perceived Health Risk –Tobacco Sticks Pack with Surgeon General's Warnings: Arm 3 (A) and with PMI Warning: Arm 4 (B) in THS-PBA-05-RRC2-US

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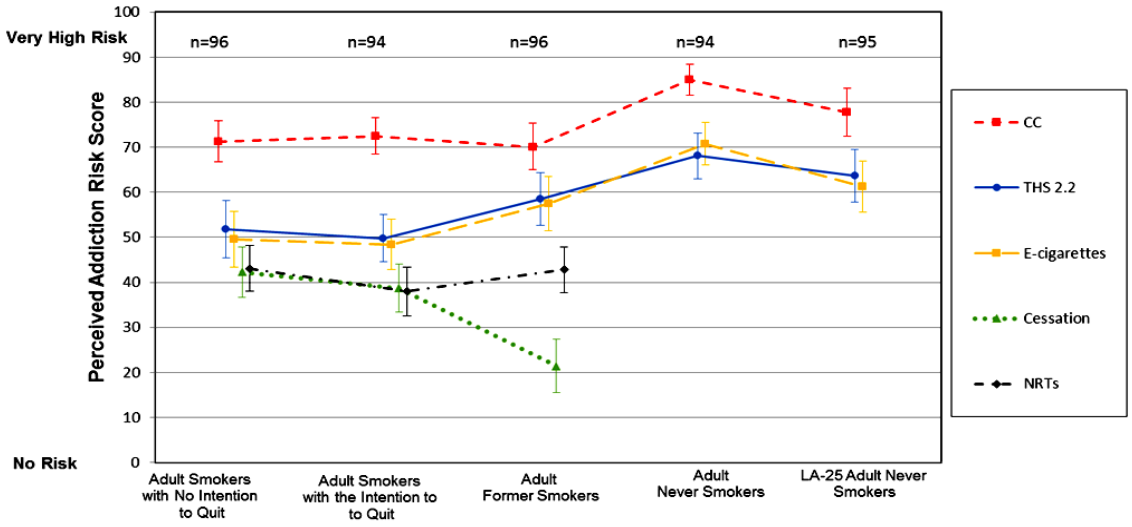
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A



HeatSticks Pack, SG warnings (Arm 3)

B



HeatSticks ™ Pack, PMI Warning (Arm 4)

Abbreviations: CC = conventional cigarette; LA = legal age; NRT = nicotine replacement therapy; THS = Tobacco Heating System.
Error bars are the 95% confidence intervals of the mean.
Note: Adult Never Smokers group includes only those Adult Never Smokers from the Main Sample.
Note: connecting lines are only to highlight clustering of outcomes for each comparator along the y-axis.
Data Source: Study Report THS-PBA-05-RRC2-US, Figure 15.1.3.2.3 and Figure 15.1.3.2.4.

Figure 11 Perceived Addiction Risk –Tobacco Sticks Pack with Surgeon General's Warnings: Arm 3 (A) and with PMI Warning: Arm 4 (B) in THS-PBA-05-RRC2-US

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6.4.4.3 THS-PBA-05-REC-US Study

Methodology

A brief description of the study methods is provided in Table 14.

Table 14 Methodology of THS-PBA-05-REC-US

Study Title: Quantitative Assessment of THS 2.2 Label, Labeling and Marketing Material with Reduced Exposure Claims
Study design: 4-cities, 5-arm parallel-group experiment. The 5 arms corresponded to 5 different combinations of communication materials and warning type, each of the materials being tested by approximately equal numbers of subjects from different smoking status groups.
Subjects: *Full Sample* (N=2272) stratified into Adult Smokers with no Intention to Quit CC (N=479), Adult Smokers with the Intention to Quit CC (N=479), Adult Former Smokers (N=480) and Adult Never Smokers (N=480). An additional oversampling of 480 Adult Never Smokers from the legal age of smoking to 25 years of age (*LA-25 Adult Never Smokers*) which includes 126 Adult Never Smokers from the *Main Sample*.
Main criteria for inclusion: • Aged 18 and above, or above state legal smoking age if above 18 years • Adult Smokers with no Intention to Quit CC[a]: currently smoking some days or every day, started more than 30 days ago with no intention to quit within 6 months; Adult Smokers with Intention to Quit CC[a]: currently smoking some days or every day, started more than 30 days ago with the intention to quit within 6 months; Adult Former Smokers: quit smoking CCs more than 30 days ago; Adult Never Smokers: never smoked or never smoked daily and less than 100 CC
Methods: <u>Comprehension</u> Closed questions on Global and Specific comprehension of THS communication materials [THS-PBA-05-REC-US Study Report Appendix 16.1.1] <u>Risk Perception</u> The PRI-Personal Risk (PRI-P) [A732 PBA01sum] composed of 3 domains: • Perceived Health Risk measured by an 18-item scale • Perceived Addiction Risk measured by a 7-item scale • Perceived Harm to Others measured by 2 single items
Criteria for Evaluation: <u>Level of Comprehension</u>: Proportion of subjects correctly answering Comprehension questions, by study arm, for the Main Sample and the LA-25 Never Smoker Sample <u>Risk Perception:</u> Perceived Health Risk, Perceived Addiction Risk and Perceived Harm to Others for THS and each comparator (i.e., CC, E-cigarettes, NRTs and Cessation), by study arm and smoking status group

[a] Include Regular Smokers (smoke at least 1 CC a day) and Intermittent Smokers (between 4 and 27 days per month, with no restrictions on total number of CC smoked over that period, between 10% and 40%).
[b] Not assessed by Adult Never Smokers

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Mockup of THS Brochure, Tobacco Sticks Pack and Direct Mail were presented branded (*iQOS* for THS and *Marlboro* for the Tobacco Sticks) to the subjects with a hypothetical price for the THS device (b) (4) and for a pack of 20 Tobacco Sticks (price of a *Marlboro* pack of CC in the specific city of the research). All materials included at least the following 2 elements:

(1) Information on THS, including the modified risk claim that "*Switching completely from conventional cigarettes to the iQOS system significantly reduces your body's exposure to harmful and potentially harmful chemicals*".
(2) Warning Section (Surgeon General's warnings or PMI Important Warning)

The mockups are presented in [THS-PBA-05-REC-US Study Report Appendix 16.1.1].

Results

Comprehension

The levels of correct comprehension that *Exposure to HPHCs is significantly reduced* ranged between 46% and 72% across all study arms (Table 15). The levels of correct comprehension that "*it has not been demonstrated that switching to THS reduces the risk of tobacco-related diseases"* were low for Arm 3 (27%) and ranged between 41% and 70% across the other study arms (Table 15). With the exception of the Tobacco Sticks Pack with PMI warning (Arm 4), exposure reduction information was better comprehended when associated with Surgeon General's warnings than with PMI Warning (Table 15). In contrast, the risk of tobacco-related diseases was better comprehended when associated with the PMI Warning than Surgeon General's warnings (Table 15). Correct comprehension of specific sections of the THS communication was high across all materials and warning types (Available Evidence to Date Section: >92%; Important Warning Section: >77%; Intended User Section: >92%; Table 15).

Overall, the levels of comprehension were similar for *LA-25 Adult Never Smokers* and the *Main Sample* (see THS-PBA-05-REC-US Study Report Table 15.2.2.2.2).

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Table 15 Main Sample in THS-PBA-05-REC-US: Proportion of Subjects with Correct Global and Specific Comprehension by Material and by Warning Type

THS Communication Material	THS Brochure		Tobacco Sticks Pack		THS Direct Mail
Arm	Arm 1	Arm 2	Arm 3	Arm 4	Arm 5
Warning	SG	PMI	SG	PMI	PMI
Correct Answer	% (n) (95% CI)	% (n) (95% CI)	% (n) (95% CI)	% (n) (95% CI)	% (n) (95% CI)
Global Comprehension					
Exposure to HPHCs is significantly reduced	68.4 (262) (63.5, 73.0)	53.0 (202) (47.9, 58.1)	72.3 (276) (67.5, 76.7)	63.7 (244) (58.7, 68.5)	46.3 (177) (41.2, 51.5)
It has not been demonstrated that switching to the *iQOS* system reduces the risk of developing tobacco-related diseases compared to smoking cigarettes.	41.0 (157) (36.0, 46.1)	69.6 (265) (64.7, 74.1)	27.0 (103) (22.6, 31.7)	59.5 (228) (54.4, 64.5)	63.1 (241) (58.0, 67.9)
Specific Comprehension					
Evidence Section					
iQOS heats tobacco but does not burn it	97.4 (373) (95.3, 98.7)	95.8 (365) (93.3, 97.6)	92.9 (355) (89.9, 95.3)	(94.5 (362) (91.7, 96.6)	92.7 (354) (89.6, 95.1)
Warning Section					
iQOS contains nicotine, which is addictive	NA	91.3 (348) (88.1, 94.0)	NA	87.5 (335) (83.7, 90.6)	89.3 (341) (85.7, 92.2)
iQOS can harm your health	NA	82.9 (316) (78.8, 86.6)	NA	78.1 (299) (73.6, 82.1)	77.7 (297) (73.2, 81.8)
Intender Users Section					
iQOS is for smokers who want to continue using tobacco	94.8 (363) (92.1, 96.8)	92.1 (351) (89.0, 94.6)	NA	NA	NA

Abbreviations: CI = confidence interval; NA = not applicable; SG = Surgeon General. *iQOS* is the commercial name and registered trademark for THS
Data Source: Study Report THS-PBA-05-REC-US, Table 15.2.2.2.1.

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Risk Perception

Positioning of THS and comparators CC, E-cigarettes, NRTs and Cessation on the 2 Perceived Risk scales (Health and Addiction) was broadly consistent across the 3 THS communication materials and the 2 warning types (see Figure 12 and Figure 13 for THS Brochure, Figure 14 and Figure 15 for Tobacco Sticks Pack and THS-PBA-05-REC-US Study Report Figures 15.1.3.1 and 15.1.3.2 for THS Direct Mail).

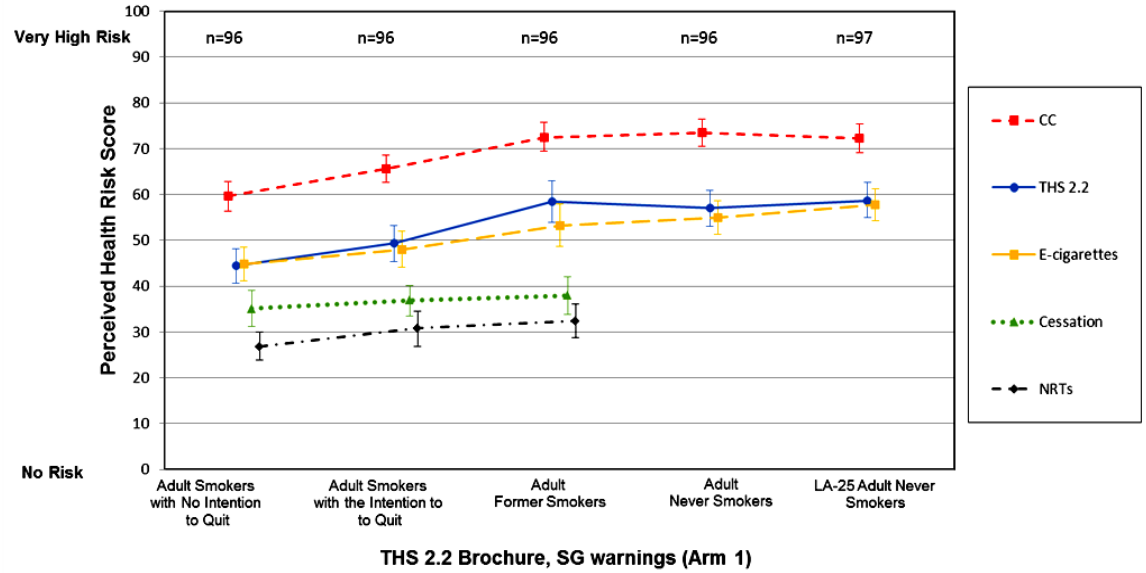
Across all smoking status groups, CC was consistently rated as having the highest *Perceived Health Risk*. Adult Smokers with no Intention to Quit CC, Adult Smokers with the Intention to Quit CC, and Adult Former Smokers, consistently rated THS with an "intermediate" *Perceived Health Risk*, below CC and above NRTs/Cessation. Across all smoking status groups, *Perceived Health Risk* ratings were similar for THS and E-cigarettes.

Adult Smokers with no Intention to Quit CC and Adult Smokers with the Intention to Quit CC rated the *Perceived Addiction Risk* of THS between the highest risk comparator (consistently CC) and the lowest comparator (NRTs or Cessation). In contrast to *Perceived Health Risk*, THS was positioned on the *Perceived Addiction Risk* scale closer to CC for Adult Former Smokers and Adult Never Smokers compared to Adult Smokers (both with and with no Intention to Quit CC). As for Comprehension assessment, perceived risk ratings were similar *for LA-25 Adult Never Smokers* and Adult Never Smokers from the *Main Sample* (THS-PBA-05-REC-US Study Report Tables 15.2.2.3.1, 15.2.2.3.2 and 15.2.2.3.3).

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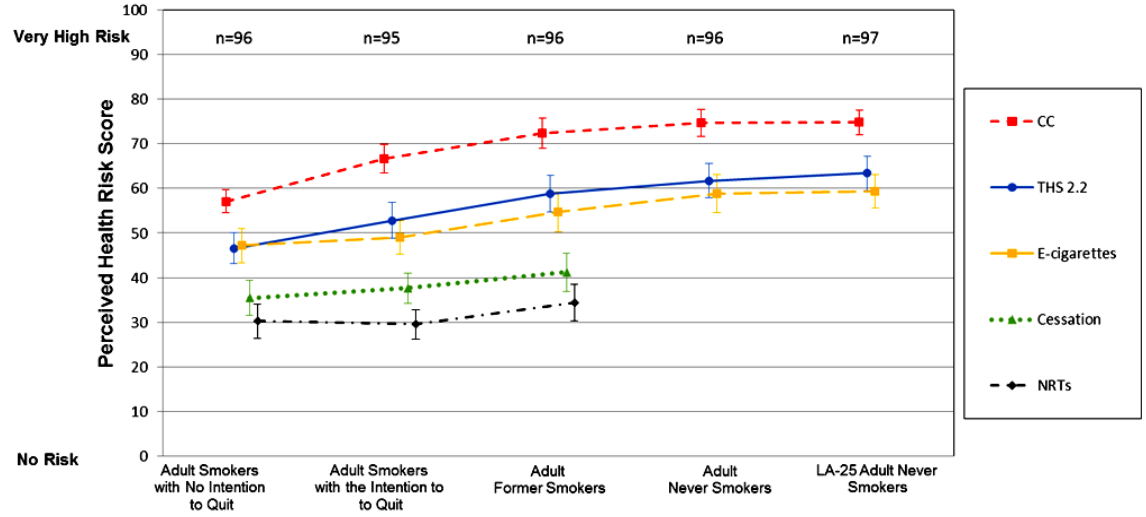
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A



THS 2.2 Brochure, SG warnings (Arm 1)

B



THS 2.2 Brochure, PMI Warning (Arm 2)

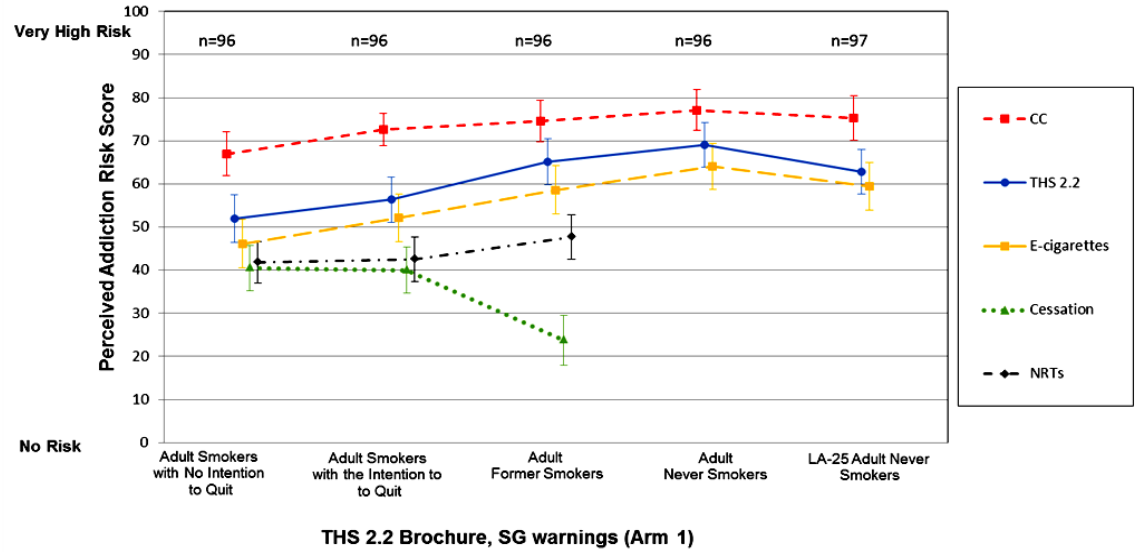
Abbreviations: CC = conventional cigarette; LA = legal age; NRT = nicotine replacement therapy; THS = Tobacco Heating System.
Error bars are the 95% confidence intervals of the mean.
Note: Adult Never Smokers group includes only those Adult Never Smokers from the Main Sample.
Note: connecting lines are only to highlight clustering of outcomes for each comparator along the y-axis.
Data Source: Study Report THS-PBA-05-REC-US, Figure 15.1.3.1.1 and Figure 15.1.3.1.2.

Figure 12 Perceived Health Risk – THS Brochure with Surgeon General's Warnings: Arm 1 (A) and with PMI Warning: Arm 2 (B) in THS-PBA-05-REC-US

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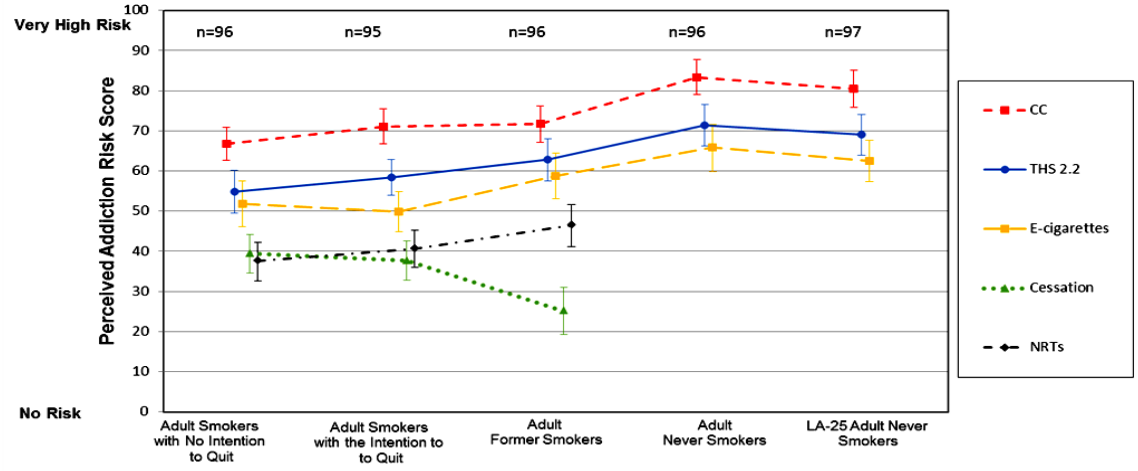
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A



THS 2.2 Brochure, SG warnings (Arm 1)

B



THS 2.2 Brochure, PMI Warning (Arm 2)

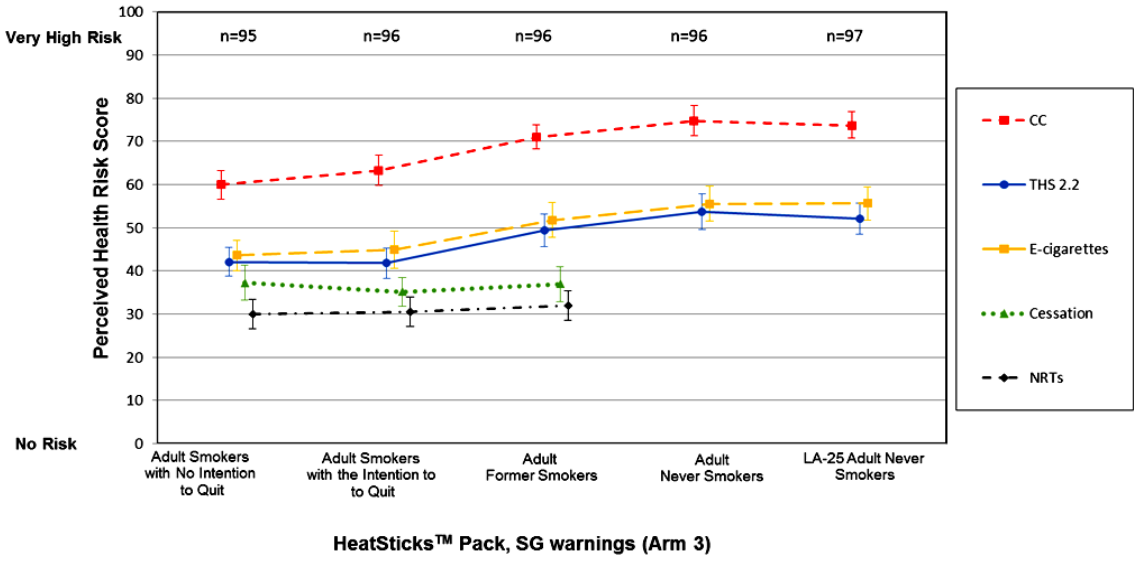
Abbreviations: CC = conventional cigarette; LA = legal age; NRT = nicotine replacement therapy; THS = Tobacco Heating System.
Error bars are the 95% confidence intervals of the mean.
Note: Adult Never Smokers group includes only those Adult Never Smokers from the Main Sample.
Note: connecting lines are only to highlight clustering of outcomes for each comparator along the y-axis.
Data Source: Study Report THS-PBA-05-REC-US, Figure 15.1.3.2.1 and Figure 15.1.3.2.2.

Figure 13 Perceived Addiction Risk – THS Brochure with Surgeon General's Warnings: Arm 1 (A) and with PMI Warning: Arm 2 (B) in THS-PBA-05-REC-US

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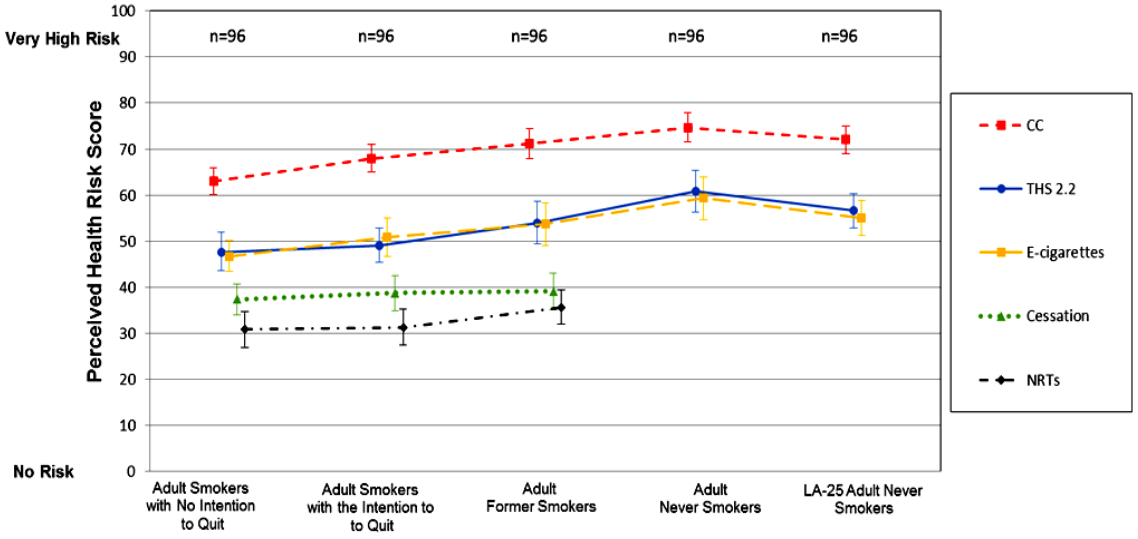
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A



HeatSticks™ Pack, SG warnings (Arm 3)

B



HeatSticks™ Pack, PMI Warning (Arm 4)

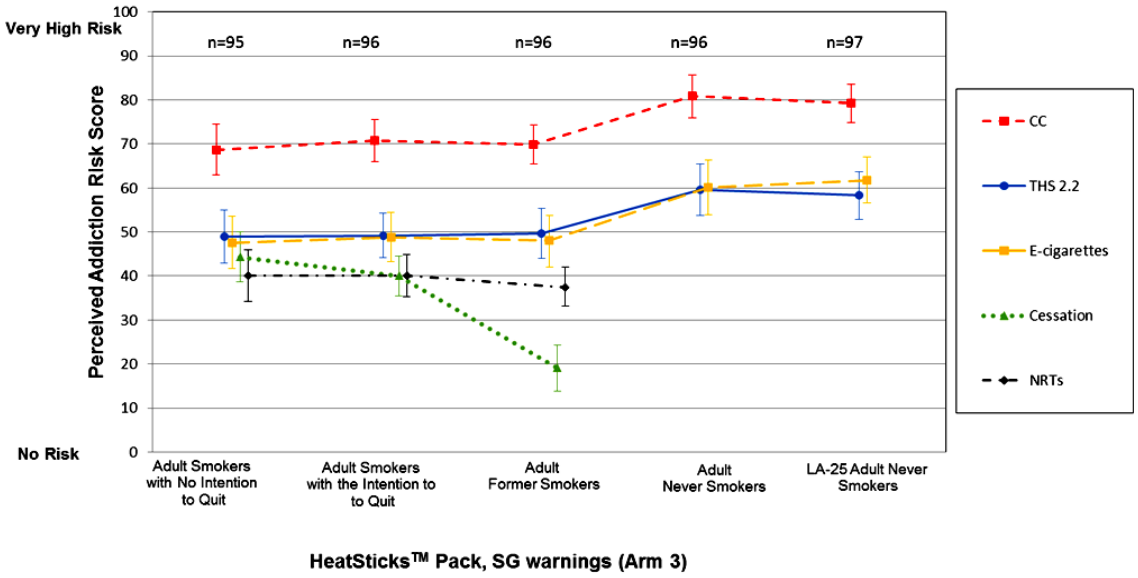
Abbreviations: CC = conventional cigarette; LA = legal age; NRT = nicotine replacement therapy; THS = Tobacco Heating System.
Error bars are the 95% confidence intervals of the mean.
Note: Adult Never Smokers group includes only those Adult Never Smokers from the Main Sample.
Note: connecting lines are only to highlight clustering of outcomes for each comparator along the y-axis.
Data Source: Study Report THS-PBA-05-REC-US, Figure 15.1.3.1.3 and Figure 15.1.3.1.4.

Figure 14 Perceived Health Risk – Tobacco Sticks Pack with Surgeon General's Warnings: Arm 3 (A) and with PMI Warning: Arm 4 (B) in THS-PBA-05-REC-US

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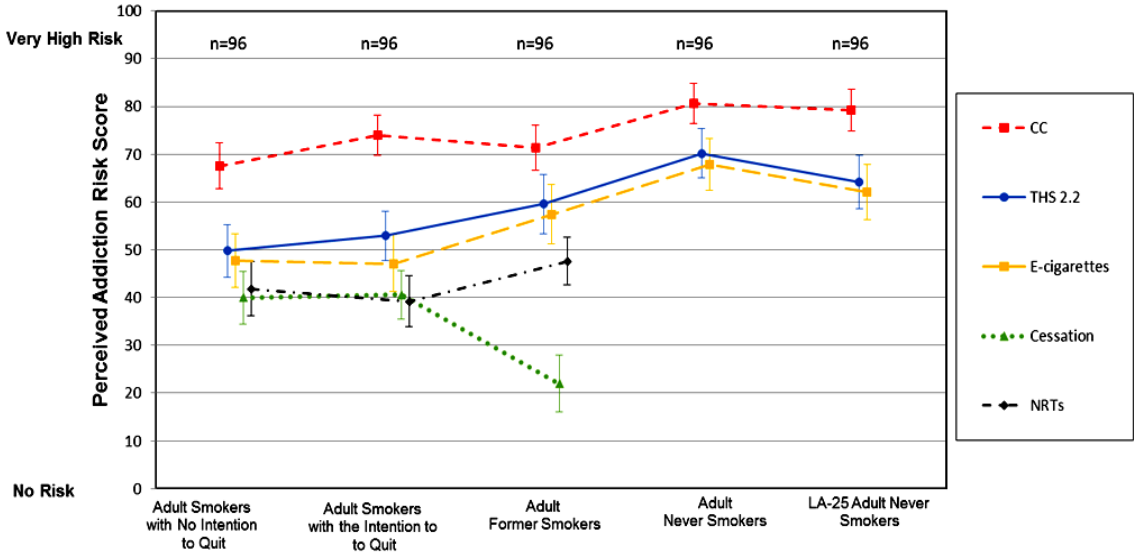
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A



HeatSticks™ Pack, SG warnings (Arm 3)

B



HeatSticks™ Pack, PMI Warning (Arm 4)

Abbreviations: CC = conventional cigarette; LA = legal age; NRT = nicotine replacement therapy; THS = Tobacco Heating System.
Error bars are the 95% confidence intervals of the mean.
Note: Adult Never Smokers group includes only those Adult Never Smokers from the Main Sample.
Note: connecting lines are only to highlight clustering of outcomes for each comparator along the y-axis.
Data Source: Study report THS-PBA-05-REC-US, Figure 15.1.3.2.3 and Figure 15.1.3.2.4.

Figure 15 Perceived Addiction Risk – Tobacco Sticks Pack with Surgeon General's Warnings: Arm 3 (A) and with PMI Warning: Arm 4 (B) in THS-PBA-05-REC-US

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6.4.5 Results across Assessment Phase Studies

6.4.5.1 Comprehension of THS Communication

Consistent with section 911 of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Family Smoking Prevention and Tobacco Control Act, the MRTP Draft Guidance states that: "*FDA must ensure, for a risk or exposure modification order, that the advertising and labeling of the MRTP enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health and in relation to all of the tobacco-related diseases and health conditions.*" (FDA (Food and Drug Administration) 2012). To address these FDA requirements, the labels, labeling and advertising materials submitted with this application underwent comprehension testing (Morris 1998). This approach was instrumental in assisting the development of effective communications ([THS-PBA-03-US]) and ensuring that none of the claims, marketing efforts, or packaging of THS submitted with this application are misleading to the consumer regarding the actual risks or benefits associated with the product's use (claim #1 [THS-PBA-05-RRC-US]; claim #2 [THS-PBA-05-RRC2-US]; claim #3 [THS-PBA-05-REC-US]).

Comprehension of Reduced Risk Information (Claims #1 and #2)

In the [THS-PBA-05-RRC-US] and [THS-PBA-05-RRC2-US] studies, evaluation of the ability of consumers to understand the reduced risk information was based on the proportion of subjects who responded correctly that *there was a reduced risk of switching from CC to THS* (*reduced risk of tobacco-related diseases* for [THS-PBA-05-RRC-US] and *reduced risk of harm* for [THS-PBA-05-RRC2-US]). As summarized in Figure 16, levels of correct comprehension were broadly consistent across the 2 studies and across the 3 types of materials (i.e., THS Brochure, Tobacco Sticks Pack, and THS Direct Mail), with a majority of subjects who responded correctly (ranged between56% to 78%). As seen on Figure 16, in both studies, the second most frequent response was that *disease/harm risk of switching from CC to THS is "the same"* (between 12% and 32% across studies and communication materials). This result pattern seems to reflect skeptical reactions from some subjects, in the sense that the reduced risk claims may have been comprehended but were difficult to believe. Of importance, only a small proportion of subjects indicated that THS is risk free (not more than 6% for each of the communication materials in each of the [THS-PBA-05-RRC-US] and [THS-PBA-05-RRC2-US] studies).

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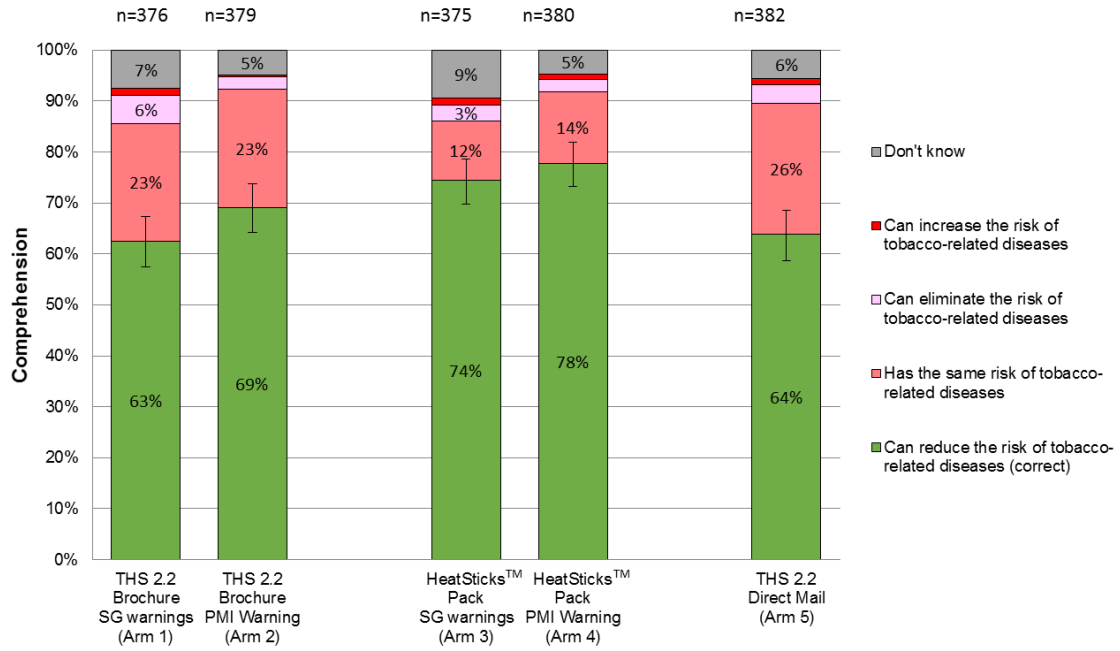
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All together, these findings across the 2 variations of reduced risk claims and the different communication materials consistently provide evidence that the THS communication on reduced risk proposed in this MRTPA are not misleading consumers with regards to the potential risk reduction of switching from CC to THS. Rather, results reveal that THS communications with reduced risk claims mostly lead to either an accurate or conservative understanding of the risk of THS. This is further supported by the high levels of correct comprehension of the THS risks as specified in the PMI Important Warning (e.g., "THS contains nicotine, which is addictive": between 87% and 92% of correct comprehension in the *Main Sample*; "The best way to reduce the risk of tobacco-related diseases is to completely quit tobacco use", between 83% and 91% in the *Main Sample*). Altogether, the findings on *Comprehension* are indicative of THS communications being clear, well comprehended, and providing appropriate information on risk reduction to enable consumers to understand the relative significance of such information in relation to the diseases and health-impacts associated with the use of tobacco products.

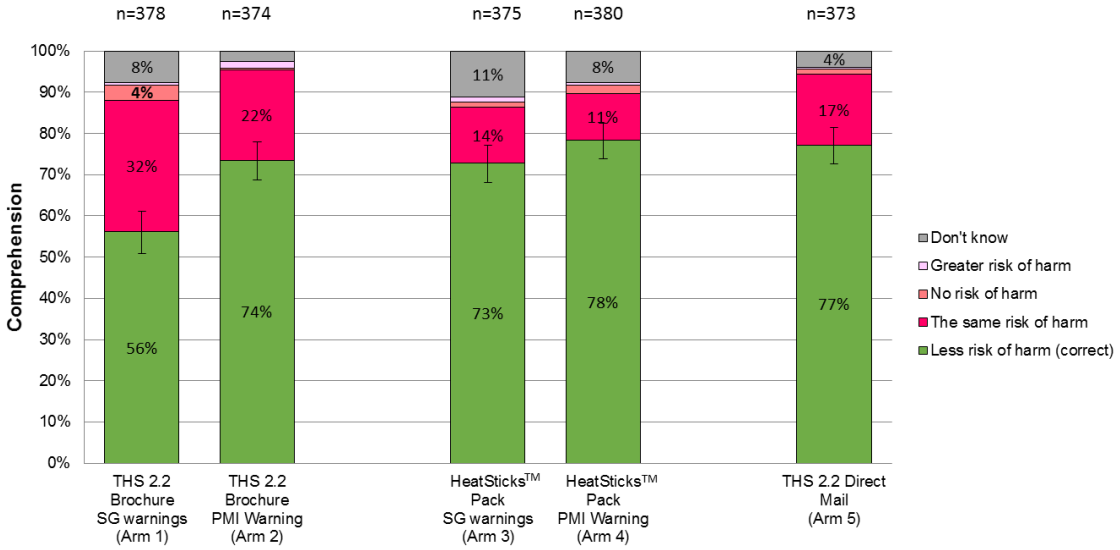
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A



B



Abbreviation: SG, Surgeon General.
Note: Error bars presented are 95% confidence intervals of the proportion correct. The 5 responses options to the Global Comprehension question on reduced risk information are presented in the Figure box caption.
Data Source: THS-PBA-05-RRC-US Study Report Figure 15.1.2.2.2; THS-PBA-05-RRC2-US Study Report Figure 15.1.2.2.1.

Figure 16 Comprehension of Reduced Risk Information for THS-PBA-05-RRC-US (A) and THS-PBA-05-RRC2-US (B) within the Main Sample

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Comprehension of Reduced Exposure Information (Claim #3)

Per the MRTP Draft Guidance, FDA recognizes that there can be "*challenges to constructing appropriate claim language that conveys the potential benefits of the product to tobacco users and does not convey that the product is less harmful than other tobacco products*" (lines 1041 to 1043), (FDA (Food and Drug Administration) 2012).

As for reduced risk claims, comprehension of the information on reduced exposure was assessed for several variations of communication across the PBA program. Thus, building upon the results of the development phase, 1 communication with reduced exposure claim was tested in [THS-PBA-05-REC-US], using the same types of marketing materials than in [THS-PBA-05-RRC-US] and [THS-PBA-05-RRC2-US], i.e., THS Brochure, Tobacco Sticks Pack, and THS Direct Mail.

In [THS-PBA-05-REC-US], evaluation of the ability of consumers to understand the reduced exposure information was based on the level of correct comprehension of 2 key communication objectives: (i) "*Exposure to harmful and potentially harmful chemicals is significantly reduced compared to conventional cigarettes"* and (ii) "*It has not been demonstrated that switching to THS reduces the risk of developing tobacco-related diseases compared to smoking conventional cigarettes*." The key statement related to the second communication objective[4] was contained in the PMI Important Warning. This statement was developed to explicitly address the FDA MRTP Draft Guidance, which states that, for an Exposure Modification Order, applicants must demonstrate that labeling and marketing does not "*mislead consumers into believing that the product is or has been demonstrated to be less harmful…. than one or more other commercially marketed tobacco products*" (lines 801–804, (FDA (Food and Drug Administration) 2012). Because this statement on risk of tobacco-related diseases occurred only in the PMI Important Warning, subjects exposed to materials with Surgeon General's warnings (Arm 1 and 3) were not presented with this statement. Thus, the design of the [THS-PBA-05-REC-US] study allowed for a comparison of comprehension that a reduced exposure claim does not necessarily imply reduced disease risk when this is explicitly stated (as in Arm 2 and 4) and when it is not (as in Arm 1 and 3).

Figure 17 summarizes, by study arm, the comprehension level of reduced exposure to HPHCs and Figure 18 the comprehension level of risk of tobacco-related diseases compared to conventional cigarettes.

Comprehension level of reduced exposure to HPHCs: the proportion of subjects who responded correctly that "*Exposure to HPHCs is significantly reduced for THS compared to CC"* ranged from 46% to 72%. Across all study arms, the second most frequent response was that "*Exposure to HPHCs is reduced by a small amount"* (between 11% and 20% across study arms, Figure 17). This indicates that a clear majority of subjects had a clear understanding that HPHC levels with THS compared to CC were reduced (between 67% and 83% across study arms, Figure 17), although evidently some subjects

[4] "It has not been demonstrated that switching to the iQOS system reduced the risk of developing tobacco-related diseases compared to smoking conventional cigarettes"

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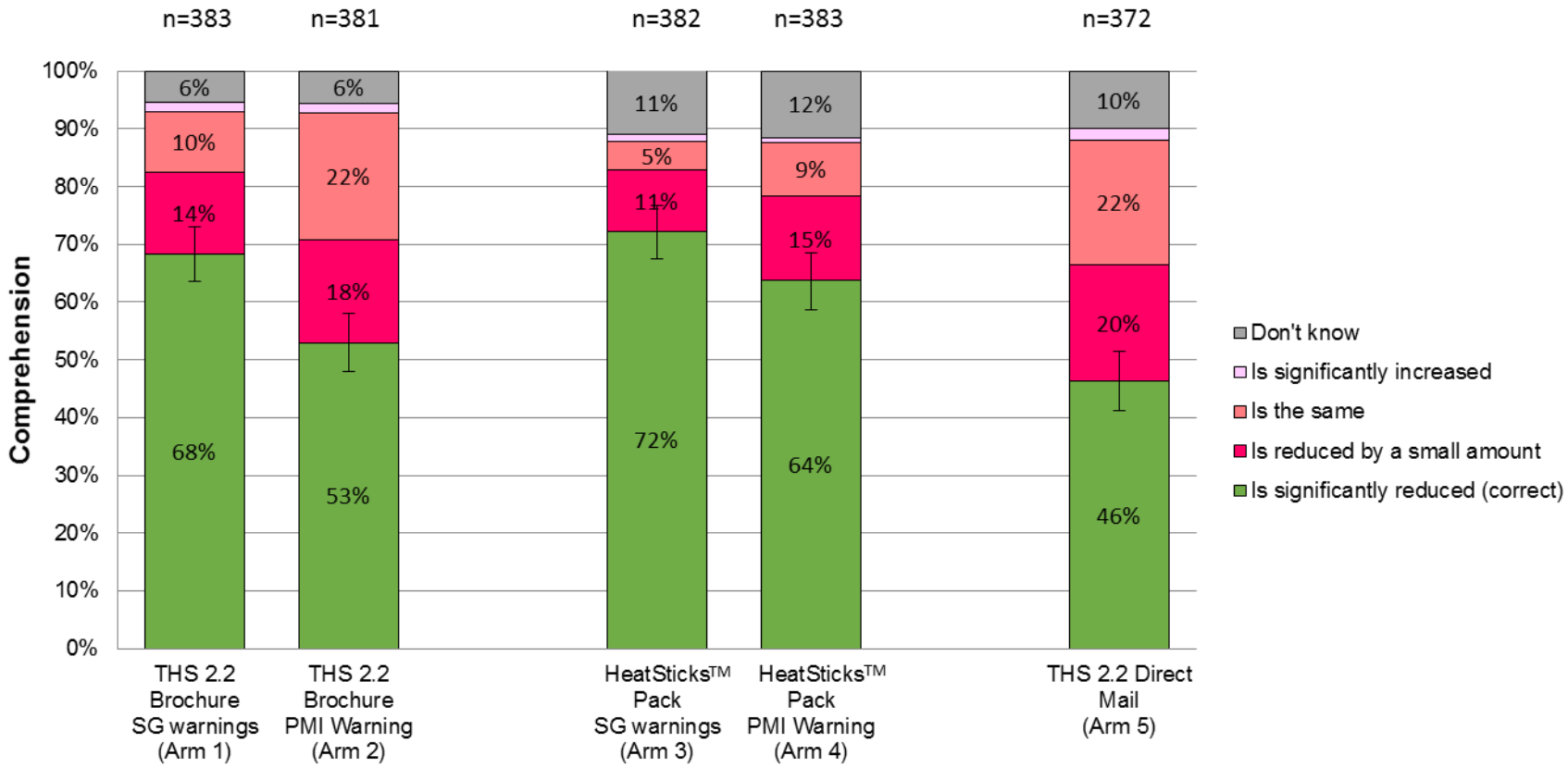
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interpreted the information concerning the degree of reduction in exposure to HPHCs in a conservative direction (underestimated the level of exposure reduction). Similar results were found in [THS-PBA-05-RRC-US], which tested communications with reduced risk claims (see [THS-PBA-05-RRC-US] Study Report Figure 15.1.2.2.1). Thus, these findings highlight a general challenge of communicating the magnitude of reduced exposure to HPHCs in a language which is specific and unambiguous, yet still easily comprehensible for the general population.

Comprehension level of risk of tobacco-related diseases compared to conventional cigarettes (Figure 18)*:* levels of correct comprehension were lower for materials containing the Surgeon General's warnings (Arm 1: 41% and Arm 3: 27%, Figure 18) than for materials with the PMI Important Warning (Arm 2: 70%; Arm 4: 60%; and Arm 5: 63%, Figure 18). These results confirm that comprehension of the statement that *reduced risk had not been demonstrated* was likely to have been enhanced by its presence as an explicit statement that is part of the PMI Important Warning. Independently from the warning type, a substantial proportion of subjects across all study arms incorrectly indicated that switching to THS "reduces the risk of developing tobacco-related diseases compared to smoking cigarettes" (44% and 58% in Arm 1 and 3 respectively; and 26%, 28%, and 28% for Arms 2, 4, and 5, respectively, Figure 18). These findings are consistent with the statement in the FDA MRTP Draft Guidance that "*FDA acknowledges that there may be challenges to constructing appropriate claim language that conveys the potential benefits of the product to tobacco users and does not convey that the product is less harmful than other tobacco products*." Our results underline the difficulty in communicating that a reduction in exposure to HPHCs does not necessarily imply a reduction in disease risk. The fact that many subjects interpreted a reduction of HPHCs as implying a reduction in disease risk in the [THS-PBA-05-REC-US] study was also observed in qualitative studies [THS-PBA-02-US] and [THS-PBA-04-US]. In these 2 studies, subjects stated that the communications on reduced exposure were clearly written and understandable, but some subjects' comments suggested that there was ambiguity in the overall communication, citing the available evidence to date (which leads to the expectation that switching to THS may potentially reduce the health risk when compared to CC) and important warning elements of the claims (there is no link between the reduction in the production of, or exposure to, harmful or potentially harmful chemicals and the reduction of the risk of developing tobacco-associated diseases) to be contradictory.

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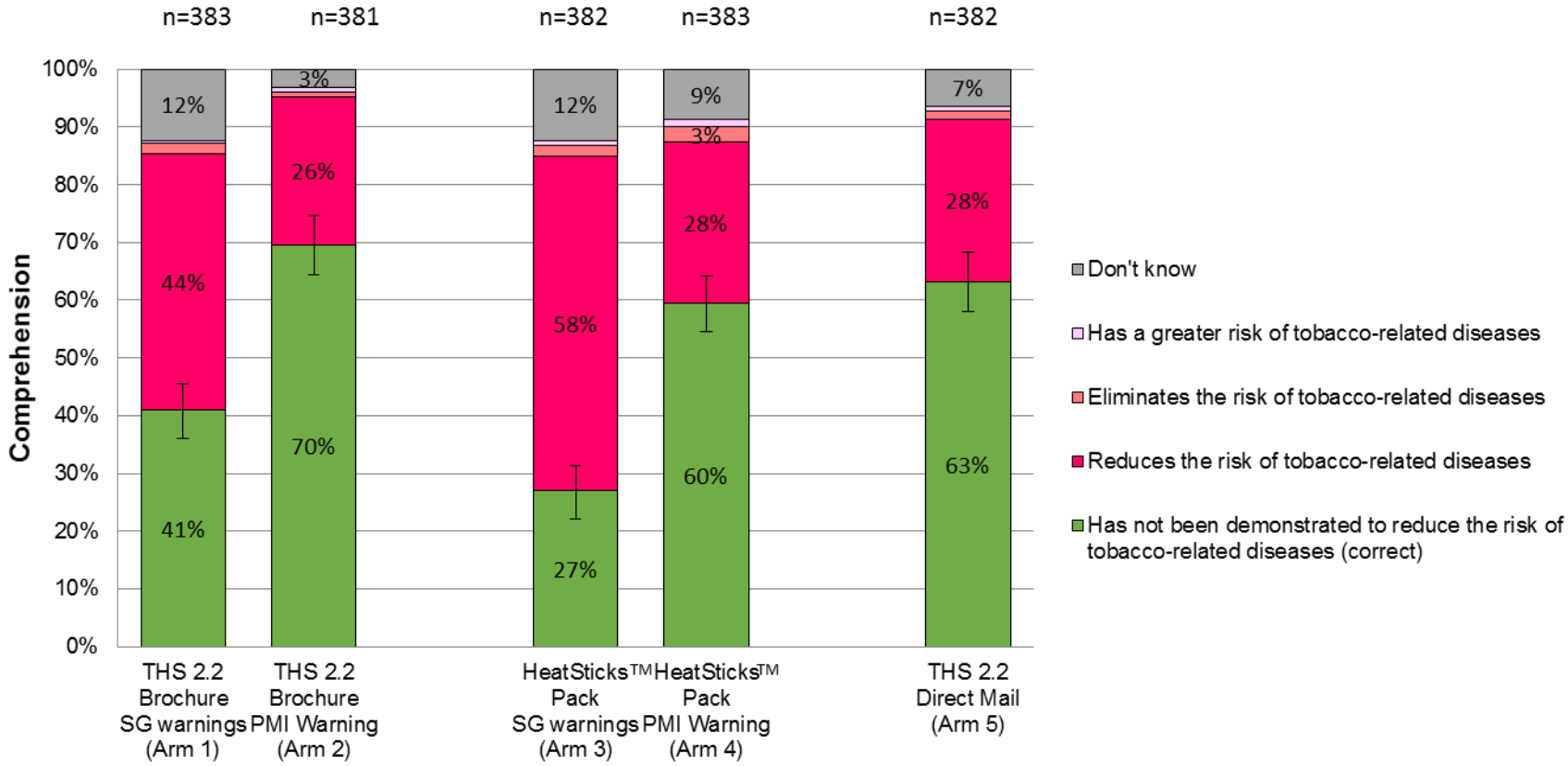


Abbreviation: SG, Surgeon General.
Note: Error bars presented are 95% confidence intervals of the proportion correct. The 5 responses options to the Global Comprehension question on reduced risk information are presented in the Figure box caption.
Data Source: THS-PBA-05-REC-US Study Report Figure 15.1.2.2.1

Figure 17 Comprehension of Reduced Exposure Information within the Main Sample of THS-PBA-05-REC-US

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Abbreviation: SG, Surgeon General.
Note: Error bars presented are 95% confidence intervals of the proportion correct. The 5 responses options to the Global Comprehension question on reduced risk information are presented in the Figure box caption.
Data Source: THS-PBA-05-REC-US Study Report Figure 15.1.2.2.2

Figure 18 Comprehension of disease-risk within the Main Sample of THS-PBA-05-REC-US

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Association between Comprehension of the Modified Risk Information and Warning Type

Across the 3 PBA-05 assessment studies, PMI Important Warning and Surgeon General's warnings were associated with similar comprehension levels across the different materials tested (i.e., THS Brochure, Tobacco Sticks Pack, and THS Direct Mail). At the same time, for the 2 studies that tested communication with reduced risk claims ([THS-PBA-05-RRC-US] and [THS-PBA-05-RRC2-US]), higher levels of correct comprehension of disease risk were found for the THS Brochure when associated with the PMI Important Warning, than when associated with Surgeon General's warnings (Figure 16). This was found despite of the fact that the information on disease risk for THS was contained within the main body of the THS Brochure, which was identical between Arm 1 and Arm 2, and not referred to in either type of warning. Likewise, in the study testing THS communications with a reduced exposure claim ([THS-PBA-05-REC-US]), disease risk information was consistently better comprehended when presented in materials with PMI Important Warning compared to materials with Surgeon General's warnings (Figure 17). An explanation could be that the combination of the claim with the PMI Important Warning reflects a coherent set of information concerning reduced risk. This may be particularly relevant for marketing materials such as the THS Brochure, where the warning appears 7 times[5] in the material.

6.4.5.2 Risk Perception based on THS Communication

An important factor in evaluating the full potential of any candidate MRTP on public health is to understand the perceived risk of the product, as this perception might be a crucial determinant of future use behavior among both current tobacco users and non-users (Ajzen 1991, Bandura 1989)). The ability of measuring perceptions of risks of using an MRTP in comparison to existing tobacco products, cessation aids, and quitting tobacco use, in both consumers who do and do not currently use tobacco products, is an important consideration for the FDA, as highlighted in their Draft Guidance (FDA (Food and Drug Administration) 2012).

In all quantitative studies conducted in the PBA program, *Risk Perception* was assessed for THS and comparators (i.e., CC, E-cigarettes, NRTs, and Cessation) using the PRI, a new self-report instrument developed by PMI. The PRI provides a reliable and valid measure, underpinned by appropriate psychometric properties, to compare different tobacco and nicotine-containing products on a "perceived risk" continuum for health outcomes (*Perceived Health Risk*) and addiction potential (*Perceived Addiction Risk*).

Perceived Health Risk

Table 16 and Table 18 summarize, for the THS Brochure and Tobacco Sticks Pack respectively, the *Perceived Health Risk* scores by product, for all smoking groups within the Main Sample, across the 3 PBA-05 studies. Within each of the smoking groups, CC was rated consistently with the highest perceived risk (THS Brochure: ranging from 59.6 to 74.7 on a 0 to 100 risk scale, Table 16; Tobacco Sticks Pack: ranging from 59.9 to

[5] *The placement of the warnings followed PM USA's internal guidelines developed and adopted for CC warning placement in the USA.*

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76.6, Table 18). Across the 3 PBA-05 studies, within current smokers (with and with no intention to quit) and former smokers, THS was consistently rated with an "intermediate" perceived health risk (THS Brochure: ranging from 42.4 to 63.2; Tobacco Sticks Pack: ranging from 40.9 to 55.6). Finally, THS and E-cigarettes had received similar *Perceived Health Risk* ratings.

Perceived Addiction Risk

Table 17 and Table 19 summarize, for the THS Brochure and Tobacco Sticks Pack respectively, the *Perceived Addiction Risk* scores by product, for all smoking groups, across the 3 PBA-05 studies. Within Adult Smokers with no Intention to Quit CC and Adult Smokers with the Intention to Quit CC, THS was consistently rated on *Perceived Addiction Risk* between the highest risk comparator (consistently CC) and the lowest comparator (consistently NRTs or Cessation). In addition, the differences of *Perceived Addiction Risk* of THS compared to CC were consistently smaller for Adult Former Smokers and Adult Never Smokers compared to the group of current smokers (Adult Smokers with and with no Intention to Quit Smoking), regardless of the type of material, claim or warning.

Perceived Harm to Others

Results for *Perceived Harm to Others* were broadly consistent with the 2 other domains of the PRI-P. For all smoking status groups, the level of *Perceived Harm to Others* for CC was consistently the highest (both for *Harming others through second hand smoke* and *Harming baby due to use during pregnancy*), with THS and E-cigarettes having similar levels of *Perceived Harm to Others* at levels between CC and NRTs (THS-PBA-05-RRC-US Study report Table 15.2.2.3.3; THS-PBA-05-RRC2-US Study report Table 15.2.2.3.3, THS-PBA-05-REC-US Study report Table 15.2.2.3.3).

Risk Perception of Young Adult Never Smokers

Overall, the 3 assessment studies provide consistent evidence that LA-25 Adult Never Smokers have similar patterns of *Risk Perception* for tobacco-related objects to those of Adult Never Smokers of all ages (THS-PBA-05-RRC-US Study report Table 15.2.2.3.1, Table 15.2.2.3.2, and Table 15.2.2.3.3; THS-PBA-05-RRC2-US Study report Table 15.2.2.3.1, Table 15.2.2.3.2, and Table 15.2.2.3.3; THS-PBA-05-REC-US Study report Table 15.2.2.3.1, Table 15.2.2.3.2, and Table 15.2.2.3.3).

Perceived Risks and Smoking Status

Through the development and assessment phase, we found strong evidence indicating effects of smoking status group on overall *Risk Perception*, and this regardless of the type of claim, warning, and communication materials. Results showed that Never Smokers (including LA-25 Never Smokers) had consistently higher *Risk Perception* scores than smokers with no Intention to Quit (e.g., Table 16, Table 17, Table 18, and Table 19 for THS Brochure and Tobacco Sticks Pack material Arms). Such an effect is consistent with the literature on risk perception (Weinstein 1999) and demonstrates construct validity of the PRI to discriminate subpopulations where differences in risk perception are expected.

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Table 16 Perceived Health Risk Scores based on THS Brochure–Main Sample by Study, Assessment Phase

Group	Product	THS-PBA-05-RRC-US						THS-PBA-05-RRC2-US						THS-PBA-05-REC-US					
		SG warnings			PMI Warning			SG warnings			PMI Warning			SG warnings			PMI Warning		
		n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI
S ITQ	CC	94	67.4	(64.3, 70.5)	93	68.4	(65.0, 71.8)	92	65.5	(62.3, 68.7)	92	66.2	(63.2, 69.1)	96	65.7	(62.7, 68.6)	94	66.6	(63.4, 69.9)
	E-cig	83	48.6	(43.9, 53.2)	82	49.6	(45.6, 53.6)	83	46.2	(41.8, 50.5)	88	48.2	(44.8, 51.7)	77	48.0	(44.1, 52.0)	85	49.0	(45.3, 52.7)
	THS	90	48.3	(44.1, 52.6)	84	53.0	(49 3, 56.8)	90	49.4	(45.7, 53.2)	87	49.3	(45.8, 52.8)	84	49.3	(45.3, 53.3)	86	52.8	(48.8, 56.8)
	NRT	89	33.4	(29.4, 37.4)	85	34.5	(30 9, 38.0)	87	32.9	(29.2, 36.6)	90	31.4	(28.0, 34.8)	88	30.8	(27.4, 34.1)	85	29.5	(26.1, 32.8)
	Cessation	94	38.7	(34.2, 43.3)	93	40.4	(37.0, 43.8)	92	38.1	(34.6, 41.6)	91	37.8	(34.5, 41.2)	95	36.9	(33.0, 40.7)	92	37.6	(34.3, 40.9)
S NITQ	CC	92	60.8	(57.8, 63.8)	93	64.2	(61.0, 67 5)	94	60.6	(56.8, 64.3)	96	61.5	(58.2, 64.8)	94	59.6	(56.3, 62.8)	95	57.1	(54.6, 59.7)
	E-cig	83	42.3	(39.2, 45.4)	87	48.7	(44 5, 52 9)	84	40.4	(36.9, 43.9)	88	45.1	(40.9, 49.3)	83	44.8	(41.2, 48.5)	85	47.2	(43.3, 51.0)
	THS	89	43.0	(39.2, 46.8)	91	47.0	(43.0, 50 9)	88	42.4	(38.7, 46.2)	90	48.6	(44.8, 52.5)	85	44.4	(40.6, 48.1)	87	46.6	(43.1, 50.0)
	NRT	88	30.6	(27.1, 34.1)	88	30.0	(26 2, 33.8)	84	25.5	(22.1, 28.8)	91	31.7	(27.9, 35.4)	87	26.9	(23.0, 30.8)	82	30.2	(26.3, 34.2)
	Cessation	91	39.4	(35.7, 43.1)	94	37.4	(33 9, 41.0)	92	35.8	(32.0, 39.6)	95	37.3	(33.6, 40.9)	92	35.1	(32.1, 38.1)	92	35.4	(31.6, 39.2)
FS	CC	92	70.9	(67.7, 74.1)	92	72.3	(68.7, 75.8)	94	70.6	(67.3, 73.8)	92	73.8	(70.4, 77.3)	96	72.5	(69.4, 75.7)	96	72.4	(69.0, 75.8)
	E-cig	75	52.3	(47.3, 57.4)	80	54.9	(50.0, 59.7)	81	51.5	(46.9, 56.1)	81	58.7	(54.1, 63.3)	81	53.3	(48.7, 57.9)	82	54.8	(50.3, 59.2)
	THS	87	52.0	(47.6, 56.4)	86	57.2	(53 3, 61 2)	83	55.2	(50.7, 59.8)	84	63.2	(58.2, 68.2)	86	58.5	(54.0, 63.0)	89	58.9	(54.8, 63.0)
	NRT	76	35.2	(30.5, 40.0)	81	34.9	(30 9, 38 9)	85	31.2	(27.3, 35.1)	84	37.5	(33.0, 42.1)	84	32.5	(28.4, 36.5)	83	34.4	(30.0, 38.7)
	Cessation	94	35.2	(31.1, 39.3)	91	38.2	(34.6, 41.7)	93	39.2	(36.4, 42.0)	92	38.1	(34.6, 41.7)	96	38.0	(34.3, 41.6)	94	41.2	(37.1, 45.2)
NS	CC	95	71.0	(67.7, 74.2)	95	72.6	(69 1, 76 1)	92	73.5	(70.8, 76.2)	91	75.6	(72.2, 79.0)	96	73.5	(70.6, 76.5)	95	74.7	(71.6, 77.8)
	E-cig	90	55.5	(51.2, 59.7)	87	55.9	(52.6, 60 1)	81	58.0	(54.3, 61.7)	84	58.3	(53.6, 63.0)	85	55.0	(51.3, 58.7)	83	58.9	(54.6, 63.1)
	THS	92	55.8	(51.8, 59.8)	91	60.7	(56.4, 65.0)	89	61.2	(57.1, 65.3)	91	62.5	(57.9, 67.0)	88	57.0	(53.1, 60.9)	89	61.7	(57.9, 65.6)

CC = conventional cigarette; CS ITQ = Current Smoker with Intention to Quit; CS NITQ = Current Smoker with no Intention to Quit; E-cig = E-cigarette; FS = Former Smoker; NRT = nicotine replacement therapy; NS = Never Smoker; RRC = reduced risk claim (claim #1; RRC2 = reduced risk claim 2 (claim #2); REC = reduced exposure claim (claim #3); THS = Tobacco Heating System.
Data Source: Study Reports THS-PBA-05-RRC-US, Table 15.2.2.3.1; THS-PBA-05-RRC2-US, Table 15.2.2.3.1; THS-PBA-05-REC-US, Table 15 2.2 3 1.

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Table 17 Perceived Addiction Risk Scores based on THS Brochure–Main Sample by Study, Assessment Phase

Group	Product	THS-PBA-05-RRC-US						THS-PBA-05-RRC2-US						THS-PBA-05-REC-US					
		SG warnings			PMI Warning			SG warnings			PMI Warning			SG warnings			PMI Warning		
		n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI
CS ITQ	**CC**	94	77.2	(73 2, 81 3)	93	77.0	(73.2, 80.8)	92	72.8	(68.4, 77.1)	93	73.0	(69.1, 77.0)	96	72.6	(68.9, 76.3)	94	71.1	(66.8, 75.5)
	E-cig	85	53.8	(48.4, 59 2)	82	56.7	(51.5, 62.0)	86	51.0	(45.7, 56.2)	90	53.5	(48.5, 58.5)	84	52.2	(46.7, 57.7)	87	49.9	(44.8, 54.9)
	THS	85	58.6	(53 1, 64 2)	87	59.5	(54.4, 64.6)	90	54.1	(49.1, 59.1)	86	54.7	(49.7, 59.7)	84	56.4	(51.1, 61.6)	85	58.4	(53.9, 62.9)
	NRT	87	47.0	(41.7, 52 3)	86	44.6	(39.7, 49.6)	87	44.6	(39.5, 49.7)	89	42.3	(37.1, 47.5)	85	42.5	(37.2, 47.9)	87	40.6	(35.7, 45.6)
	Cessation	94	43.1	(38.0, 48 3)	93	45.5	(40.8, 50.2)	93	41.9	(37.0, 46.8)	90	40.3	(35.8, 44.9)	94	40.0	(34.9, 45.1)	93	37.6	(32.9, 42.3)
CS NITQ	**CC**	93	68.6	(63.7, 73 5)	94	72.3	(67.8, 76.8)	95	64.4	(59.3, 69.5)	96	69.5	(64.8, 74.3)	95	67.0	(62.0, 72.0)	94	66.7	(62.6, 70.8)
	E-cig	85	43.5	(38.4, 48.7)	86	51.5	(46.2, 56.9)	82	42.5	(37.0, 48.0)	89	48.3	(43.3, 53.2)	87	46.1	(40.5, 51.8)	86	51.8	(46.1, 57.5)
	THS	86	50.8	(45.7, 55 9)	87	54.9	(49.8, 60.1)	87	44.2	(38.9, 49.5)	88	51.6	(46.3, 56.9)	84	52.0	(46.5, 57.5)	87	54.9	(49.5, 60.2)
	NRT	84	39.7	(34.6, 44.7)	88	44.8	(39.3, 50.2)	80	34.7	(29.1, 40.2)	90	40.7	(35.8, 45.7)	86	41.8	(36.6, 47.0)	85	37.5	(32.7, 42.3)
	Cessation	92	45.8	(40.7, 50.8)	93	44.4	(38.5, 50.3)	92	40.7	(34.7, 46.6)	93	44.8	(39.5, 50.0)	92	40.5	(35.7, 45.3)	93	39.4	(34.5, 44.2)
FS	**CC**	93	67.3	(62 1, 72.6)	92	75.0	(70.2, 79.7)	93	69.0	(63.9, 74.1)	92	72.0	(66.9, 77.1)	96	74.5	(69.8, 79.3)	96	71.7	(67.2, 76.2)
	E-cig	80	51.2	(45.0, 57 5)	86	59.3	(53.7, 64.9)	83	51.2	(44.7, 57.8)	86	60.0	(54.1, 65.9)	88	58.6	(53.0, 64.2)	86	58.8	(53.1, 64.5)
	THS	88	58.1	(52.0, 64 1)	87	64.4	(59.0, 69.9)	85	58.8	(52.4, 65.2)	88	62.5	(57.0, 68.0)	93	65.1	(59.8, 70.4)	92	62.9	(57.6, 68.1)
	NRT	77	41.7	(35.6, 47.8)	86	48.5	(43.4, 53.5)	85	46.8	(40.7, 53.0)	88	50.1	(44.4, 55.8)	89	47.7	(41.9, 53.4)	86	46.4	(40.5, 52.3)
	Cessation	94	24.6	(19 3, 29.8)	94	28.1	(22.7, 33.4)	93	26.7	(21.7, 31.7)	92	25.7	(20.7, 30.7)	96	23.8	(18.6, 28.9)	96	25.1	(19.8, 30.4)
NS	**CC**	93	73.8	(68 5, 79 2)	92	77.3	(73.0, 81.6)	92	76.7	(71.7, 81.7)	90	80.6	(76.1, 85.2)	95	77.1	(72.4, 81.8)	96	83.4	(79.0, 87.8)
	E-cig	89	62.9	(57.0, 68.7)	89	65.6	(60.3, 70.8)	87	62.2	(56.7, 67.8)	87	65.9	(60.3, 71.5)	88	64.1	(58.8, 69.4)	90	65.8	(59.9, 71.6)
	THS	88	63.7	(57.7, 69.8)	91	67.9	(62.8, 73.1)	90	63.0	(57.3, 68.7)	88	71.5	(66.2, 76.8)	93	69.0	(63.8, 74.2)	93	71.4	(66.2, 76.5)

CC = conventional cigarette; CS ITQ = Current Smoker with Intention to Quit; CS NITQ = Current Smoker with no Intention to Quit; E-cig = E-cigarette; FS = Former Smoker; NRT = nicotine replacement therapy; NS = Never Smoker; RRC = reduced risk claim (claim #1; RRC2 = reduced risk claim 2 (claim #2); REC = reduced exposure claim (claim #3); THS = Tobacco Heating System.
Data Source: Study Reports THS-PBA-05-RRC-US, Table 15.2.2.3.1; THS-PBA-05-RRC2-US, Table 15.2.2.3.1; THS-PBA-05-REC-US, Table 15 2.2 3 1.

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Table 18 Perceived Health Risk Scores based on Tobacco Sticks Pack–Main Sample by Study, Assessment Phase

Group	Product	THS-PBA-05-RRC-US						THS-PBA-05-RRC2-US						THS-PBA-05-REC-US					
		SG warnings			PMI Warning			SG warnings			PMI Warning			SG warnings			PMI Warning		
		n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI
CS ITQ	**CC**	93	65.3	(62.6, 67 9)	96	67.5	(64.5, 70.6)	96	66.6	(63.5, 69.7)	94	67.9	(64.7, 71.0)	96	63.3	(59.8, 66.8)	94	68.0	(65.0, 71.0)
	E-cig	82	45.5	(42.0, 48 9)	91	47.8	(43.9, 51.7)	89	44.7	(41.0, 48.4)	85	48.6	(44.9, 52.3)	82	44.9	(40.6, 49.2)	80	50.9	(46.7, 55.1)
	THS	81	43.3	(39.8, 46.8)	92	48.2	(44.6, 51.9)	85	44.4	(40.7, 48.1)	85	47.5	(43.8, 51.3)	82	41.8	(38.3, 45.3)	86	49.1	(45.4, 52.8)
	NRT	85	29.5	(26 2, 32 9)	89	33.9	(30.0, 37.8)	93	30.6	(27.0, 34.3)	90	31.9	(28.6, 35.3)	86	30.5	(27.1, 33.9)	90	31.3	(27.5, 35.1)
	Cessation	91	38.3	(34 3, 42.4)	96	36.4	(33.1, 39.6)	95	41.8	(38.1, 45.4)	93	36.9	(33.4, 40.5)	94	35.1	(31.7, 38.5)	92	38.8	(34.9, 42.8)
CS NITQ	**CC**	93	63.5	(60 5, 66 5)	95	61.8	(58.7, 64.9)	94	61.3	(57.8, 64.7)	96	63.5	(60.5, 66.5)	95	59.9	(56.6, 63.2)	96	63.1	(60.2, 66.0)
	E-cig	84	43.3	(39.7, 46 9)	84	45.3	(41.4, 49.1)	86	42.2	(38.1, 46.4)	85	43.8	(39.6, 48.0)	84	43.6	(40.1, 47.1)	88	46.8	(43.4, 50.1)
	THS	83	40.9	(37.8, 44 1)	88	46.3	(42.8, 49.8)	83	41.3	(37.0, 45.6)	89	44.7	(40.7, 48.7)	87	42.1	(38.8, 45.4)	84	47.7	(43.6, 51.9)
	NRT	86	28.8	(25 5, 32 2)	89	29.9	(26.1, 33.6)	84	28.6	(24.3, 32.8)	90	27.9	(23.8, 31.9)	86	29.9	(25.9, 34.0)	86	30.9	(27.5, 34.3)
	Cessation	90	36.9	(32 9, 40.8)	93	38.0	(34.7, 41.4)	92	39.0	(35.5, 42.6)	95	38.0	(34.3, 41.7)	94	37.2	(33.8, 40.6)	93	37.4	(33.5, 41.3)
FS	**CC**	93	69.9	(66.6, 73 3)	93	71.7	(68.3, 75.1)	92	72.6	(69.0, 76.2)	96	73.9	(70.6, 77.2)	96	71.0	(68.3, 73.8)	94	71.2	(68.0, 74.5)
	E-cig	78	50.9	(46.8, 55 1)	74	51.8	(47.4, 56.1)	78	52.1	(47.6, 56.5)	84	53.2	(48.6, 57.8)	84	51.8	(47.7, 55.9)	79	53.7	(49.1, 58.3)
	THS	82	49.4	(45 3, 53 5)	79	52.3	(48.5, 56.1)	76	53.1	(48.1, 58.1)	81	55.6	(51.1, 60.1)	82	49.3	(45.6, 53.1)	86	54.0	(49.5, 58.6)
	NRT	77	31.5	(27 5, 35 5)	75	30.8	(26.5, 35.0)	77	32.6	(28.4, 36.8)	87	34.5	(30.4, 38.5)	86	32.0	(27.9, 36.1)	88	35.7	(31.7, 39.7)
	Cessation	93	34.9	(31.6, 38 2)	93	37.6	(33.6, 41.6)	89	38.5	(34.1, 42.8)	95	37.0	(33.1, 40.9)	94	36.9	(33.5, 40.3)	95	39.1	(35.5, 42.8)
NS	**CC**	93	75.4	(72.4, 78 3)	93	76.6	(73.4, 79.7)	93	75.9	(72.7, 79.1)	94	75.6	(72.6, 78.6)	94	74.8	(71.3, 78.3)	96	74.7	(71.6, 77.9)
	E-cig	85	58.0	(54.0, 62.0)	88	63.8	(59.6, 67 9	84	59.9	(55.6, 64.2)	85	60.9	(56.8, 65.0)	77	55.5	(51.5, 59.6)	87	59.4	(54.7, 64.0)
	THS	88	54.7	(50 5, 58 9)	85	63.0	(58.8, 67.3)	86	58.4	(53.5, 63.3)	85	59.8	(55.6, 64.0)	81	53.7	(49.6, 57.8)	90	60.9	(56.4, 65.4)

CC = conventional cigarette; CS ITQ = Current Smoker with Intention to Quit; CS NITQ = Current Smoker with no Intention to Quit; E-cig = E-cigarette; FS = Former Smoker; NRT = nicotine replacement therapy; NS = Never Smoker; RRC = reduced risk claim (claim #1; RRC2 = reduced risk claim 2 (claim #2); REC = reduced exposure claim (claim #3); THS = Tobacco Heating System.
Data Source: Study Reports THS-PBA-05-RRC-US, Table 15.2.2.3.1; THS-PBA-05-RRC2-US, Table 15.2.2.3.1; THS-PBA-05-REC-US, Table 15 2.2 3 1.

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Table 19 Perceived Addiction Risk Scores based on Tobacco Sticks Pack–Main Sample by Study, Assessment Phase

Group	Product	THS-PBA-05-RRC-US						THS-PBA-05-RRC2-US						THS-PBA-05-REC-US					
		SG warnings			PMI Warning			SG warnings			PMI Warning			SG warnings			PMI Warning		
		n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI	n	Mean	95% CI
CS ITQ	**CC**	93	75.0	(71 2, 78.8)	95	74.8	(70.1, 79.5)	96	72.9	(69.1, 76.7)	94	72.5	(68.5, 76.5)	95	70.8	(65.9, 75.6)	94	73.9	(69.8, 78.1)
	E-cig	86	46.7	(41.4, 52.0)	89	49.7	(44.0, 55.3)	89	53.0	(48.1, 57.9)	84	48.4	(42.8, 54.1)	85	48.8	(43.2, 54.4)	81	47.1	(41.2, 53.1)
	THS	81	44.9	(40.0, 49.8)	88	52.1	(46.0, 58.2)	88	54.5	(49.4, 59.5)	84	49.8	(44.6, 55.0)	84	49.2	(44.1, 54.3)	85	52.9	(47.7, 58.0)
	NRT	85	40.6	(35 5, 45.7)	87	45.7	(40.1, 51.3)	91	45.4	(40.7, 50.2)	88	38.0	(32.7, 43.4)	84	40.1	(35.5, 44.6)	88	39.2	(34.1, 44.3)
	Cessation	90	45.0	(40.0, 50.0)	96	38.6	(33.3, 43.9)	94	45.2	(40.1, 50.2)	93	38.7	(33.3, 44.0)	94	40.0	(35.2, 44.8)	92	40.6	(35.3, 45.9)
CS NITQ	**CC**	93	70.2	(65 1, 75 3)	95	70.5	(65.8, 75.3)	94	67.5	(62.4, 72.5)	96	71.2	(66.7, 75.8)	95	68.7	(62.9, 74.5)	95	67.5	(62.7, 72.4)
	E-cig	84	45.0	(39 5, 50.4)	85	47.4	(41.7, 53.1)	87	48.5	(43.4, 53.6)	88	49.6	(43.4, 55.8)	86	47.5	(41.6, 53.5)	83	47.7	(42.1, 53.4)
	THS	83	48.9	(43.4, 54 3)	87	54.2	(49.0, 59.4)	80	44.8	(39.3, 50.2)	87	51.8	(45.5, 58.1)	88	48.9	(42.9, 54.9)	84	49.8	(44.3, 55.3)
	NRT	84	40.5	(35 2, 45.8)	87	38.1	(33.1, 43.1)	84	42.8	(37.6, 48.0)	89	43.1	(37.5, 48.7)	90	40.1	(34.5, 45.8)	85	41.8	(36.3, 47.2)
	Cessation	90	46.3	(41.0, 51.6)	93	43.0	(38.0, 48.0)	92	39.7	(34.8, 44.6)	94	42.3	(37.2, 47.4)	94	44.3	(38.5, 50.1)	91	40.0	(34.3, 45.7)
FS	**CC**	93	65.6	(60 5, 70.6)	94	70.2	(65.3, 75.2)	92	68.1	(62.7, 73.4)	96	70.1	(65.0, 75.3)	96	69.9	(65.4, 74.4)	96	71.3	(66.6, 76.0)
	E-cig	82	52.6	(47 2, 58.0)	80	54.0	(48.7, 59.3)	80	54.5	(48.8, 60.3)	88	57.5	(51.5, 63.5)	86	48.0	(42.1, 53.8)	87	57.4	(51.3, 63.6)
	THS	79	48.4	(42.6, 54 2)	83	55.8	(50.4, 61.2)	80	54.6	(48.6, 60.5)	88	58.5	(52.6, 64.4)	84	49.7	(44.0, 55.4)	91	59.6	(53.4, 65.7)
	NRT	83	41.9	(36.7, 47 2)	78	46.0	(40.1, 51.9)	76	45.3	(39.3, 51.3)	89	42.8	(36.9, 48.8)	89	37.5	(32.2, 42.7)	89	47.6	(41.7, 53.5)
	Cessation	93	20.8	(16 3, 25 3)	93	27.3	(22.2, 32.5)	90	24.1	(18.4, 29.8)	96	21.4	(16.3, 26.5)	95	19.1	(14.7, 23.6)	96	22.0	(17.1, 27.0)
NS	**CC**	93	79.2	(74.4, 83 9)	93	84.6	(80.6, 88.5)	93	77.4	(72.5, 82.2)	88	85.0	(81.5, 88.5)	91	80.8	(75.9, 85.7)	96	80.7	(76.5, 84.9)
	E-cig	89	61.7	(55.4, 67 9)	88	72.8	(68.1, 77.6)	89	62.0	(56.3, 67.6)	88	70.7	(66.0, 75.5)	83	60.2	(53.9, 66.4)	92	67.8	(62.4, 73.2)
	THS	89	59.0	(53.0, 65.0)	90	72.5	(67.5, 77.4)	85	61.7	(55.8, 67.7)	91	68.1	(62.9, 73.2)	83	59.6	(53.7, 65.5)	94	70.2	(65.0, 75.4)

CC = conventional cigarette; CS ITQ = Current Smoker with Intention to Quit; CS NITQ = Current Smoker with no Intention to Quit; E-cig = E-cigarette; FS = Former Smoker; NRT = nicotine replacement therapy; NS = Never Smoker; RRC = reduced risk claim (claim #1; RRC2 = reduced risk claim 2 (claim #2); REC = reduced exposure claim (claim #3); THS = Tobacco Heating System.
Data Source: Study Reports THS-PBA-05-RRC-US, Table 15.2.2.3.1; THS-PBA-05-RRC2-US, Table 15.2.2.3.1; THS-PBA-05-REC-US, Table 15 2.2 3 1.

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6.4.6 Overall Conclusions

To assess the full potential of an MRTP, demonstration of individual-level risk reduction is not sufficient. Having a reduced-risk product on the market may be beneficial to the individual smoker switching into it from CC, but it could also have a negative impact on the population as a whole by encouraging non-smokers to use the MRTP or current smokers intending to quit choosing the MRTP instead of quitting altogether. In a pre-market setting, an important factor to assess the full potential of an MRTP is to measure consumer understanding and perception associated with the product, as these might be crucial determinants of future use (IOM (Institute of Medicine) 2012). In particular, a critical concern is ensuring that the product label, labeling and advertising material provide an accurate, balanced, and non misleading picture of the product's characteristics that permits consumers to understand the risks of using the product compared to other tobacco products and thus allow them to make informed decisions about product use (Hatsukami 2012).

The overall results from the PBA program provide consistent evidence on the appropriateness of the proposed claims, labeling and advertising submitted in this MRTPA in terms of consumer understanding and perceptions. These conclusions are drawn from a multistep approach using mixed methods ([THS-PBA-02-US] and [THS-PBA-04-US] qualitative studies; [THS-PBA-03-US], [THS-PBA-05-RRC-US], [THS-PBA-05-RRC2-US], and [THS-PBA-05-REC-US] quantitative studies) to provide on the one hand, in depth information on how consumers understand and perceive THS communication, and on the other hand, precise estimates of comprehension and risk perception, using validated methods developed on the basis of accepted standards (FDA (Food and Drug Administration) 2010, FDA (Food and Drug Administration) 2009).

6.4.6.1 Ability of Consumers to Understand the Modified Risk Claims

Findings of THS-PBA-05-RRC (testing Claim #1: "Reduced risks of tobacco-related diseases") and THS-PBA-05-RRC2 (testing Claim #2: "Reduced risk of harm") show that adult smokers and adult non-smokers have an accurate understanding that THS presents less risk than CC (levels of comprehension between 64% and 78% for THS-PBA-05-RRC and between 56% and 78% for THS-PBA-05-RRC2, respectively), is not free of risk (not more than 6% and 4% of the participants answered that using THS has no risk, for each of the communication materials in THS-PBA-05-RRC and THS-PBA-05-RRC2, respectively), and is an addictive product because it contains nicotine (levels of comprehension between 87% and 90% for THS-PBA-05-RRC and between 88% and 92% for THS-PBA-05-RRC2, respectively). This accurate understanding was also found for the group of adult never smokers from legal smoking age to 25 years of age, demonstrating that young adults did not have a different understanding of THS communication than older consumers. In turn, these results are consistent with the expectation that the public should be informed and should understand that THS is not a risk-free product, in particular young adults, who are particularly susceptible to try new tobacco products.

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The skepticism expressed by some study participants who reported that THS has the same risk than CC (between 11% to 32% of subjects across marketing materials and studies) may be explained by several factors, perhaps with the lack of awareness and knowledge about THS being the most likely one. These findings are in line with the literature on alternative tobacco products such as smokeless tobacco products, indicating a general misconception among consumers regarding the relative harmfulness of noncombustible products (Borland 2012, Pepper 2015). Consumers do not have the necessary knowledge to discriminate the harm of every (or each) non-combustible products in comparison to cigarettes. Educating consumers about THS is an essential aspect to gain acceptance from smokers to switch to THS and an effective and accurate communication provided by product manufacturer constitutes an important strategy to achieve this.

The ability of consumers to understand modified risk information will have some significance only if this generates appropriate consequences on consumer behavior. As demonstrated in Sections 6.2.2 and 6.3.1, THS communications generated a substantial intent to use among adult smokers (positive intention to use THS on a regular basis ranged between 23% and 39% for [THS-PBA-05-RRC-US] and between 20% and 38% for [THS-PBA-05-RRC2-US]) while not encouraging adult non-smokers to use the product (positive intention to use THS ranged between 0% and 6% for [THS-PBA-05-RRC-US] and between 0% and 5% for PBA-05-RRC2-US). These results indicate that THS communication with an accurate and scientifically substantiated reduced risk claim (Claim #1 or Claim #2) provides consumers with balanced and non misleading information, thus generating the intended behavior in both adult smokers and adult non-smokers.

The overall results of [THS-PBA-05-REC-US] (testing Claim #3: "Reduced body's exposure to harmful and potentially harmful chemicals") demonstrate that consumers (including adult non-smokers) were able to understand that, upon switching from CC to THS, they would benefit from a reduction of exposure to harmful and potentially harmful chemicals (levels of comprehension between 46% and 72%), even though a quarter of the study participants tended to interpret the degree of reduction in a conservative manner (between 11% and 20% answered that the level of HPHCs was reduced by a small amount despite the reduction being qualified as "significant" in the message).

In contrast, understanding that *it has not been demonstrated that switching to THS reduces the risk of developing tobacco-related diseases compared to smoking conventional cigarettes* was characterized by a considerable variability and achieved lower level of comprehension. This was particularly true for communication materials containing the currently mandated Surgeon General warnings (41% and 27% and correctly responded that it has not been demonstrated to reduce the risk of tobacco-related diseases for Brochure and Tobacco Stick Pack, respectively) compared to the PMI Important Warning (comprehension levels of 70%, 60% and 63% for the brochure, Tobacco Stick Pack and Direct Mail, respectively). The challenge in appropriately communicating the reduced toxicity of an MRTP without conveying that the product is less harmful than other tobacco products has been acknowledged by The FDA in the MRTP Draft Guidance (lines 1041 to 1043, (FDA (Food and Drug Administration)

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2012). Evidence from earlier generation of products, referred to as potential reduced exposure products (PREPs) by the IOM (Stratton 2001), shows that, despite the absence of explicit reduced health risk claims, consumers tend to over-interpret information on the reduced toxicity of PREPs as an indication of reduction in health risks (Hamilton 2004, O'Connor 2005, Pederson 2007, Shiffman 2004). Even if the information on reduced toxicity is valid, the fact that it can interpreted as the product being less risky, especially by those who would otherwise quit smoking or those who do not use tobacco products, could result in tobacco product use. Findings described in detail in Sections 6.2.2 and 6.3.1, indicate that adult smokers do not change their intention to quit smoking after being exposed to THS labeling and advertising. Moreover THS labeling and advertising generates low interest in adult former smokers, and very low in adult never smokers of any age, regardless of the type of claim. Thus, the findings support the conclusion that a reduced exposure claim will not have a negative impact on tobacco use in non-intended populations. Post-market studies are needed to corroborate the above finding and draw definitive conclusions. Findings of [THS-PBA-05-REC-US] assessing the currently mandated Surgeon General warnings and the PMI Important Warning, indicate that the presence of an explicit statement that "*it has not been demonstrated that switching to THS reduces the risk of developing tobacco-related diseases compared to smoking conventional cigarettes*" improves considerably the likelihood that consumers will not over-interpret reduced exposure as reduced risk. The reduced exposure information was about twice as likely to be understood correctly when presented with the PMI Important Warning compared to the Surgeon General's warnings (levels of comprehension between 60 and 70% for materials including PMI Important warning; levels of comprehension between 27% and 41% for materials including Surgeon General's warnings). Overall, these results highlight the importance of educating smokers and non-smokers about the potential risks of alternative products compared to CC. This can be achieved through accurate communication of scientifically substantiated and non-misleading claims, backed-up with the adequate regulation and authorization from regulatory agencies, as proposed in the FDA Draft Guidance on MRTPs.

6.4.6.2 Consumers' Beliefs about the Risks of Using the Product

FDA recommends applicants to submit scientific studies assessing consumers' beliefs about the health risks of using the product relative to other tobacco products, cessation aids, and quitting all tobacco use. The reliability and validity of risk perception measures have been repeatedly questioned as the different strategies that have been proposed so far to measure consumers' risk perceptions do not meet regulatory standards for validated methods (Rees 2009). Typically, a first approach is to assess risk perception with a single direct measure of comparative harm (e.g., (Ambrose 2014, O'Connor 2005, Parascandola 2009, Pearson 2016). However, such relative perceived risk assessment is of limited use if multiple products are to be compared. A second approach is to indirectly compare absolute measures of risk perception, i.e. when several products are assessed separately one at a time (e.g., (Blake 2015, Hamilton 2004, Pepper 2015, Rodu 2015). Indirect measures have been found to be more discriminative than direct measures (Wackowski 2016). The majority of these measures are, either direct or indirect, based on a single summary item or few items, focusing on the global harmfulness of tobacco

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products, e.g. "how harmful is this product? Acknowledging the lack of robust and validated measurement instruments, PMI has undertaken, as part of the PBA program, the development and psychometric validation of a new measurement instrument, the Perceived Risk Instrument (PRI). The project consisted of a step-wise approach including qualitative research (literature review, focus groups, expert opinion, and cognitive debriefing interviews) and 2 quantitative testings, following the current best practice guidelines (Aaronson 2002, Mokkink 2010), including the US FDA scientific requirements for Patient-Reported Outcomes (FDA 2009), (more details can be found in [A732PBA01Sum]). The PRI implemented in studies allows the comparison on the same metric, of both Perceived Health Risk and Perceived Addiction Risk across different tobacco products (e.g., CC, e-cigarettes), NRTs and Cessation, and across consumers with different smoking habits (e.g. current smokers, former smokers, never smokers).

In that context, due to the difference in the assessment method, findings presented in this application may be difficult to put in perspective with results reported in recent studies on risk perception of different tobacco products (Ambrose 2014, Blake 2015, Pearson 2012, Pepper 2014, Pepper 2015, Rodu 2015, Yong 2016, Zhu 2013). However, the reliability and validity of our findings rely on the sensitivity of the measurement instrument rather than on the consistency with the scientific literature, which allow for robust conclusions to be drawn with regards to the perceived risks of THS in comparison with other tobacco products.

Perceived Risks of THS in Comparison to other Tobacco Products

Findings from the 6 studies conducted on risk perception of THS (i.e. [THS-PBA-02-US], [THS-PBA-03-US], [THS-PBA-04-US], [THS-PBA-05-RRC-US], [THS-PBA-05-RRC2-US], [THS-PBA-05-REC-US]) show that THS is perceived as less risky than CC which is considered by far as the most risky tobacco product. While this finding was expected when THS was associated with a reduced risk claim, the fact that THS was also associated with lower ratings than CC when associated with a reduced exposure claim, highlights once again the difficulty in communicating the concept that a reduction in exposure to HPHCs does not necessarily imply a reduction in disease risk. These findings are consistent with the statement in the MRTP Draft Guidance that "*FDA acknowledges that there may be challenges to constructing appropriate claim language that conveys the potential benefits of the product to tobacco users and does not convey that the product is less harmful than other tobacco products.*" On average, THS was approximately between 8 and 22 points lower than CC on the 0 to 100 *Perceived Health Risk Scale*, considering all materials and claims. Qualitative findings provided further insights on how this lower risk perception was formed. Consumers understood that THS is a tobacco product and, as such, stated that there is a health risk associated with using it, even though the heating process was expressed by consumers as a plausible and compelling explanation to infer that the risks of THS were lower compared to CC. In complement of the non-clinical and clinical evidence submitted in this application, these findings are supportive of the potential for THS to be used as an alternative to CC by current adult smokers.

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Risk perception of e-cigarettes and THS were very close, both on *Perceived Health Risk* and *Perceived Addiction Risk*. On average, the absolute difference between THS and e-cigarettes varied between 1 and 5 points and between 1 and 8 points on a 0 to 100 scale for *Perceived Health Risk* and *Perceived Addiction Risk*, respectively. Though THS and e-cigarettes do not rely on the same technology, it is conceivable that study participants may have interpreted them as similar products due to the electronic component in both types of products. Based on qualitative findings [THS-PBA-02-US], presence of tobacco in THS seems to be a key factor to trigger a slightly higher perception of risk than e-cigarettes and, while this may be the exact reason why adult smokers are attracted to use the product, it appears also to be the reason expressed by non-smokers for having no interest to try or use THS.

When comparing different smoking groups, (i.e., current smokers, former smokers and never smokers), results show high consistency on how THS was perceived compared to other tobacco products: as lower risk than CC, and as similar risk as e-cigarettes. At the same time, perception of health risk was consistently higher in non-smokers (former and never) compared to current smokers, regardless of the tobacco product. These results are in line with previous literature on perceived risk of tobacco products (Weinstein 2005) and provide further confidence in the external validity of our measurement instrument to measure perceived risks, not only for CC but also potential MRTPs. In accordance with health-related behavior models (Ajzen 1991, Bandura 1989), these results are consistent with the view that, THS is likely to have the intended consequences: attract current smokers because it is perceived less risky than CC while not causing or motivating non-users to be interested in the product because it is still considered a risky product.

Perceived Risks of THS in Comparison to Cessation Aids and Quitting all Tobacco Use

Across all 6 studies, THS was consistently rated at higher perceived health and addiction risk than NRTs and Cessation. In studies using the Perceived Risk Instrument, on average, THS was between 11 and 29 points higher than NRTs and between 2 and 25 points higher than Cessation on the 0 to 100 *Perceived Health Risk Scale*. On average, THS was between 2 and 21 points higher than NRTs and between 0 and 41 points higher than Cessation on the 0 to 100 *Perceived Addiction Risk Scale*. The higher risk perception of THS compared to NRTs is consistent with existing literature on risk perception of novel products compared to NRTs (Overland 2013, Pepper 2015) and supports the conclusions that smokers are unlikely to perceive THS as equivalent to NRTs, though some of them may see THS as a less risky alternative to CC that could help them quitting smoking. Results also suggest that, if THS is marketed as proposed, smokers who would otherwise quit tobacco use would have the correct understanding and perception from THS communication that with THS they will still encounter risk for their health and risk of remaining addicted to nicotine compared to quitting tobacco use.

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In brief, based on the weight of evidence presented in this section, it can be concluded that the claims and the THS communication proposed in this MRTPA to market THS enable U.S. consumers, both smokers and nonsmokers, to understand the modified risk information and to infer an accurate perception of the risk of using THS in comparison to other tobacco products, cessation aids and quitting tobacco.

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