International expert consensus on electronic nicotine delivery systems and heated tobacco products: a Delphi survey

Ivan Berlin,1,2 Isabelle Jacot-Sadowski,2 Jean-Paul Humair,3 Jacques Cornuz2

ABSTRACT

Objectives To provide a consensus from a panel of international experts about electronic nicotine delivery systems (ENDS) and heated tobacco products (HTP).

Design Cross-sectional survey.

Methods A Delphi survey was conducted among international experts in tobacco control and smoking cessation. The first part addressed statements or recommendations about ENDS, the second about HTP, both divided into four categories: regulation, sale, use and general issues.

Setting Experts from 15 countries.

Participants Individuals with clinical, public health or research expertise in tobacco control and/or smoking cessation.

Results 268 experts were contacted, 92 (34%) completed the first, 55/92 (60%) the second round. Consensus for ENDS: components of e-liquids, an upper limit of nicotine concentration should be defined; a warning on the lack of evidence in long-term safety and addiction potential should be stated; ENDS should not be regulated as consumer products but either as a new category of nicotine delivery or tobacco products; ENDS should not be sold in general stores but in specialised shops, shops selling tobacco or in pharmacies with restriction on sale to minors; administration of illegal drugs is likely with ENDS. Consensus for HTP: HTP have the same addictive potential as cigarettes; they should be regulated as a tobacco product with similar warning messages as cigarettes; their advertisement should not be allowed. ENDS and HTP use should not be allowed in indoor public places; a specific tax should be implemented for ENDS, taxes on HTP should not be lower than those for cigarettes; use of cigarettes is more likely with both ENDS and HTP (dual use) than quitting smoking.

Conclusions Experts in tobacco control and/or smoking cessation recommend differential regulation for ENDS and HTP. The results of this survey may be useful for health authorities, decision makers and researchers of the tobacco use and cessation field.

INTRODUCTION

The negative health effects of combusted tobacco products are undeniable and well known. In the last decade, alternative nicotine delivery systems have been marketed with the aim of helping smokers quit combustible tobacco by switching to these new nicotine delivery products. The new products include the electronic nicotine delivery systems (ENDS): (1) open system ENDS or electronic cigarettes (EC) such as cigalike/e-cigarettes, tank systems; (2) closed system ENDS or pods. Nicotine is delivered as free nicotine base at pH=7–9 or as nicotine salts at pH=3.5–6.8.1 ENDS comprise a battery, an aerosol. ENDS deliver nicotine similarly to nicotine replacement therapies in most cases, an aerosol. ENDS have the same addictive potential as cigarettes; they should be regulated as a tobacco product with similar warning messages as cigarettes; their advertisement should not be allowed. ENDS and HTP use should not be allowed in indoor public places; a specific tax should be implemented for ENDS, taxes on HTP should not be lower than those for cigarettes; use of cigarettes is more likely with both ENDS and HTP (dual use) than quitting smoking.

Conclusions Experts in tobacco control and/or smoking cessation recommend differential regulation for ENDS and HTP. The results of this survey may be useful for health authorities, decision makers and researchers of the tobacco use and cessation field.
During the same period, heated tobacco products (HTP), which are electronic devices heating tobacco, were developed, manufactured and promoted by the tobacco industry with the aim that smokers using combusted tobacco switch to HTP.

The lack of clear evidence of the benefit/risk ratio of ENDS and HTP led us to establish an experts’ consensus by the Delphi survey method. In a previous Delphi survey of 2015 among 40 Swiss experts, Blaser and Cornuz found that EC containing nicotine should be available for smokers but needed specific regulations, such as restrictions on advertisement and banning their use in public places.

Since this publication, the landscape of nicotine containing products has widened. Moreover, the previous survey reflected the consensual opinion of only Swiss experts. We felt another Delphi survey was needed enlarging its scope to HTP and experts from outside of Switzerland.

The Delphi survey approach is proposed if the information about a specific issue is contradictory or insufficient leading to individual uncertainty. To the best of our knowledge, no universal guidelines on this method exist. However, there is an agreement that its use is justified in exploring underlying assumptions or information that result in differing judgements or to generate consensus in a specific expert group. Its aim is to transform into consensus individual expert’s opinion independently of the opinion of other experts. This independence is important in protecting the respondent from the influences of fellow experts’ opinion and of dominant voices that may occur in face-to-face meetings.

This study aimed to provide a consensus from a panel of international experts about the regulation, sale, use, addiction potential of ENDS and HTP as well as research questions.

**METHODS**

**Participants**

The authors established a list of individuals with clinical, public health or research expertise in tobacco control and/or smoking cessation. An expert is a person who has special skills and/or knowledge derived from training or experience in a specific field. The authors contacted individuals who published, presented at scientific meetings about tobacco and alternative nicotine delivery systems, who were members of a scientific society for tobacco and nicotine research, had previous experience in managing smokers or were involved in public health activities in this field. We excluded collaborators, that is, coworkers of the authors because they may share the same views as the authors. Participants’ identity was kept confidential; each participant was ‘blinded’ about the other participants’ identity and the other participants’ responses. Data were collected by online web surveys (SurveyMonkey) after participants received an invitation email. Participation was voluntary and could be declined. Participants were required to declare their conflict of interest in the tobacco control/cessation field. No individuals from the tobacco industry were allowed to participate.

The number of Delphi survey rounds is usually 2 or 3. The major limitation of the addition of a fourth or a fifth round Delphi survey is the progressively increasing attrition rate as the number of rounds increases. This may lead to a progressively reduced representativeness of the first round group’s responses and consequently to a reduced validity of the consensus obtained at the last round.

For the first round, 268 experts (150 Swiss, 118 international) were contacted; 92 (34%) completed the first round survey. For the second round, all respondents of the first round were asked to complete the second round questionnaire. Results of the first round survey were summarised in the email calling to complete the second round survey as usual for Delphi surveys. With the exception of country of residency, no demographic characteristics were recorded.

The first round was launched on 13 December 2018 with a reminder on 18 January 2019 for Switzerland and on the 21 May 2019 for other countries. The second round was launched on 21 January 2020 for international experts and on 14 February 2020 for Swiss experts. After each round, 1 month was allowed to complete the surveys. It is important to note that the EC, or vaping, product use-associated lung injury (EVALI) outbreak occurred in the USA between the two rounds.

**Questionnaire**

As much as possible, the questions were similar to those used in the previous survey. The questionnaire consisted of two parts. The first part addressed statements or recommendations about ENDS, the second part addressed statements or recommendations about HTP. Both parts were divided into four categories: regulation, sale, use and general issues. The first round questionnaire included 7, 3, 3 and 8 questions about ENDS, respectively for regulation, sale, use and general issues; for HTP the number of questions was 4, 2, 2 and 7, respectively. In the first round, statements and recommendations were rated on a scale ranging from 1 to 10 where 1 meant that the respondent strongly disagreed and 10 that the respondent strongly agreed. We considered that a consensus has been reached if the mean score situated between 1–3 for negative agreement and 8–10 for positive agreement. Questions with a mean score higher than 3 and lower than 8 were considered as not having reached an agreement and were reported to the second round.

The second round included respectively 4, 4, 4 and 7 questions about ENDS and 2, 4, 2 and 7 questions about HTP on regulation, sale, use and general issues. We hypothesised that 50 to 70% of the first round respondents would complete the second round questionnaire, and this reduced number of respondents would increase variability of the response, limiting our ability to reach a consensus. We, therefore, used a different strategy in the second round questionnaire. If the question was
categorical, we asked for a binary response (agree/don’t agree). Some first round questions had several items with binary answer; we transformed these multiple item categorical responses to a hierarchical Likert scale of preference: ‘most preferred answer (1)—less preferred answer (5)’. This more constraining strategy of answers while keeping the same questions intended to make emerge more consensual answers. For binary responses we arbitrarily considered that a consensus was reached if the responses were ≤30% or ≥70%.

**Patient and public involvement**

No patients or population groups were involved.

**Data analysis**

Continuous data are described as means and SD, frequencies as numbers and per cent. When the same question was asked for ENDS and HTP, the mean score difference was calculated along with its 95% CIs. In case of several possible responses to the same question, responses were compared by a paired t-test. These comparisons are considered as secondary findings.

**RESULTS**

Ninety-two experts completed the first round survey. Most of the respondents were from Switzerland or France (table 1). Sixty per cent (N=55) of the first round respondents completed the second round questionnaire.

Table 2 shows items for which a consensus has been obtained in the first and second rounds. Numerical results are shown in online supplemental tables 1 and 2.

Consensus had already been reached after the first round on most items for the regulation and sale of ENDS: components of e-liquids should be provided on the product; an upper limit of nicotine concentration should be defined; manufacturers should respect a list of authorised components; a warning on the lack of evidence of long term safety and the addiction potential of ENDS should be stated. Sale restriction should be proposed for minors and advertisement for ENDS targeting minors, never and former smokers should not be allowed. In the second round, agreement occurred that ENDS should not be regulated as consumer products but either as a new category of nicotine delivery or as tobacco product with specific regulation or as conventional cigarettes.

Agreement has been reached that HTP should not be regulated as a consumer product but as a tobacco product. Warning messages should not be softer than those on cigarettes and their advertisement should not be allowed. Use of both ENDS and HTP should not be allowed in indoor public places.

ENDS should not be sold in general stores but preferentially in specialised shops, shops selling tobacco or in pharmacies. A consensus occurred that a specific tax be defined; manufacturers should respect a list of authorised components of e-liquids should be provided on the product; an upper limit of nicotine concentration should be defined; manufacturers should respect a list of authorised components; a warning on the lack of evidence of long term safety and the addiction potential of ENDS should be stated. Sale restriction should be proposed for minors and advertisement for ENDS targeting minors, never and former smokers should not be allowed. In the second round, agreement occurred that ENDS should not be regulated as consumer products but either as a new category of nicotine delivery or as tobacco product with specific regulation or as conventional cigarettes.

Health authorities should advise never-smokers not to use ENDS or HTP. They should encourage conventional cigarette smokers to switch to ENDS as a potential risk reduction tool but should not encourage switching from cigarettes to HTP.

Research should provide data about the long-term safety for both ENDS and HTP. Experts agreed that HTP and ENDS are a health risk for non-smokers and for smokers who quit more than 6 months ago. HTP were also considered dangerous for the health of smokers who quit within 6 months. Agreement has already been reached in the first round that HTP have the same addictive potential as conventional cigarettes; addiction associated with ENDS was considered lower than with conventional cigarettes in the second round.

Respondents considered that dual use (either ENDS or HTP use concomitantly with cigarettes) is more likely with both ENDS and HTP than quitting smoking, and that the administration of illegal drugs is likely with ENDS.

Online supplemental tables 1 and 2 provide difference scores between ENDS and HTP. The comparison of agreements concerning ENDS and HTP demonstrates that HTP was more likely to be regulated as a tobacco product than ENDS, which could also be regulated as a medication. Compared with ENDS, there was higher agreement that HTP should be sold in same places as tobacco products. There was higher agreement that ENDS, but not HTP, be sold in pharmacies or specialised shops. ENDS had higher scores than HTP for use as a first-line or second-line smoking cessation method, were considered as less dangerous for tobacco smokers, and to be less addictive than HTP.
Table 2  Summary of first and second round questionnaires items having reached a consensus

<table>
<thead>
<tr>
<th>ENDS</th>
<th>HTP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Specific regulation</strong></td>
<td><strong>Specific regulation</strong></td>
</tr>
<tr>
<td><strong>First round</strong></td>
<td><strong>Second round</strong></td>
</tr>
<tr>
<td>▶ The components of e-liquids should be stipulated on the product.</td>
<td>▶ HTP should not be regulated as a consumer product or a medication.</td>
</tr>
<tr>
<td>▶ Manufacturers and retail sellers should respect a list of authorised liquid components.</td>
<td>▶ HTP should be regulated preferentially as conventional cigarettes; it is less preferred to be regulated as a new category of nicotine delivery product (preference question).</td>
</tr>
<tr>
<td>▶ only produce or sell accepted models with specific requirements.</td>
<td>▶ The warning messages should not be softer for HTP than for conventional cigarettes.</td>
</tr>
<tr>
<td>▶ respect an upper limit of nicotine concentration in the e-liquids.</td>
<td>▶ HTP should be forbidden in indoor public places.</td>
</tr>
<tr>
<td>▶ A warning on the lack of evidence of long-term safety and the risk of addictive potential should be stated on the product.</td>
<td>▶ Advertisement for HTP should not be allowed.</td>
</tr>
<tr>
<td>▶ The use of ENDS should be forbidden in indoor public places.</td>
<td>▶ Advertisement targeting smokers should not be allowed.</td>
</tr>
<tr>
<td>▶ Advertisement should not target minors, never smokers and former smokers.</td>
<td></td>
</tr>
<tr>
<td><strong>Second round</strong></td>
<td><strong>Second round</strong></td>
</tr>
<tr>
<td>▶ ENDS should not be regulated as a consumer product but either as a new category of nicotine delivery or as tobacco product with specific regulation or as conventional cigarettes (preference question).</td>
<td>▶ ENDS should not be sold in general stores but preferentially in specialised shops or at the same places as tobacco products or in pharmacies (preference question).</td>
</tr>
<tr>
<td>▶ Manufacturers and retail sellers should indicate if they sell ENDS via tobacco industry or related retail sellers.</td>
<td>▶ Sale restriction for ENDS should concern non smokers. No agreement has been reached of their use in pregnant smokers.</td>
</tr>
<tr>
<td></td>
<td>▶ A specific tax should be implemented for ENDS.</td>
</tr>
<tr>
<td><strong>Sale</strong></td>
<td><strong>Use</strong></td>
</tr>
<tr>
<td><strong>First round</strong></td>
<td><strong>Second round</strong></td>
</tr>
<tr>
<td>▶ Sale restrictions should be proposed for minors but not for current smokers.</td>
<td>▶ Health authorities should advise never-smokers not to use ENDS.</td>
</tr>
<tr>
<td></td>
<td>▶ Health authorities should advise never-smokers not to use HTP.</td>
</tr>
<tr>
<td>▶ Health authorities should encourage conventional cigarettes smokers to switch to ENDS as a risk reduction tool.</td>
<td></td>
</tr>
<tr>
<td><strong>General issues</strong></td>
<td><strong>General issues</strong></td>
</tr>
<tr>
<td><strong>First round</strong></td>
<td><strong>Second round</strong></td>
</tr>
<tr>
<td>▶ Research should address long-term safety, dual consumption, psychological and social effects of ENDS and its efficacy as a cessation tool for quitting conventional cigarettes.</td>
<td>▶ Research should address long-term safety, dual consumption, psychological and social effects of HTP.</td>
</tr>
<tr>
<td></td>
<td>▶ HTP are dangerous for health of never smokers and former smokers who quit more than 6 months ago.</td>
</tr>
<tr>
<td></td>
<td>▶ HTP are considered as having an addictive potential similar to conventional cigarettes.</td>
</tr>
<tr>
<td>▶ The use of ENDS for administration of illegal drugs is likely.</td>
<td>▶ The likelihood of dual consumption (conventional cigarettes+HTP) is higher than quitting smoking.</td>
</tr>
<tr>
<td>▶ ENDS are considered dangerous for the health of never smokers and for smokers who quit smoking more than 6 months ago.</td>
<td>▶ The health risk related to HTP use is considered lower than that with conventional cigarettes.</td>
</tr>
<tr>
<td>▶ The likelihood of dual consumption (conventional cigarettes+ENDS) is higher than quitting smoking.</td>
<td>▶ HTP are considered dangerous for health of former smokers who quit within the 6 months.</td>
</tr>
<tr>
<td>▶ The health risk related to ENDS use is considered lower than that with conventional cigarettes.</td>
<td></td>
</tr>
<tr>
<td>▶ The addiction associated with ENDS use is considered lower than with conventional cigarettes.</td>
<td></td>
</tr>
<tr>
<td>▶ If ENDS become a popular use, it should be seen as a medical and a public health issue.</td>
<td></td>
</tr>
</tbody>
</table>

ENDS, electronic nicotine delivery systems; HTP, heated tobacco products.
DISCUSSION

Statement of the principal findings

In this Delphi survey of international experts in the tobacco control, smoking cessation and nicotine field consensus emerged for the following items:

ENDS: Components of e-liquids should be provided on the product; an upper limit of nicotine concentration should be defined; a warning on the lack of evidence in long term safety and the addiction potential of ENDS should be stated; ENDS should not be regulated as consumer products but either as a new category of nicotine delivery or tobacco products with or without specific regulation; ENDS should not be sold in general stores but either in specialised shops, shops selling tobacco or in pharmacies with sale restriction for minors.

HTP: These products have the same addictive potential than conventional cigarettes; they should not be regulated as a consumer product but as a tobacco product with similar warning messages than cigarettes; their advertisement should not be allowed.

Use of both ENDS and HTP should not be allowed in indoor public places; a specific tax should be implemented for ENDS, taxes on HTP should not be lower than those for conventional cigarettes.

A consensus was reached that use of cigarettes is more likely with both ENDS and HTP (dual use) than quitting smoking, and the administration of illegal drugs is likely with ENDS. Second round responses suggested that ENDS are more likely to be a first or second line smoking cessation aid than HTP and are less dangerous for tobacco smokers and less addictive than HTP.

Strengths and weaknesses of the study

Strengths includes the involvement of an international panel of well-known experts in tobacco control, smoking cessation. Responses were independent of other panel members’ responses. The survey addressed many questions that may be raised by healthcare professionals and decision makers in this field. The change in the structure of answers reducing the likelihood of uncertainties could have contributed to increase the likelihood of consensus.

The results and their interpretation have several limitations: (1) The low response rate (34%) for the first round and non-random selection of experts reduce the generalisability of the findings; (2) The number of respondents in the second round was about half the number of respondents of the first round, thus, the second round responses cannot be considered as reflecting the first round respondents’ opinion; (3) The questions of the second round may have forced the respondents to make a decision aiming, despite their potential uncertainty, to answer the question. This could elicit a consensus when uncertainty may still exist; (4) Between the first and second rounds, the EVALI epidemic occurred in USA and that may have influenced responses of the second round; (5) Responses represent individual opinions and do not reflect those from a specific country or group; (6) The survey lacks experts from several geographic regions, such as Asia, Africa and South-America. (7) The comparison of the results of first round, before EVALI, and second round, after EVALI could have indicated whether the results were influenced by the EVALI epidemic. However, this comparison would include several biases: (1) this within-individual comparison is against the Delphi surveys’ principles; (2) we changed the strategy of responses to converge more toward a consensus, implying that the answers’ structure is not identical; (3) this comparison would be useful if we wanted to assess the test–retest reliability of our questionnaire but this was not the aim; (4) the power would be reduced almost by half, therefore, the conclusions would be uncertain and (5) we could not ascertain that within-individual changes in answers are associated with EVALI because several other, mostly unknown or uncontrollable factors could influence answers of the second compared with the first round.

Relation to other studies and to the general context of the topic

The previous survey of our group reported consensus from Swiss experts in tobacco control and/or cessation and addressed only ENDS related issues. The current survey presents consensus among international experts and opinion on both ENDS and HTP.

To the best of our knowledge, no study was published on opinions of healthcare professionals and researchers with expertise in tobacco control and/or smoking cessation about the regulation, sale, use, health risk and addiction potential of both ENDS and HTP. A recent systematic review by Erku et al on beliefs and self-reported practices of healthcare professionals about ENDS reported wide variation in the opinions about ENDS as a smoking cessation aid. As in our survey, the majority think that ENDS are safer than cigarettes. Concerns about its short-term and long-term safety, addictiveness and gateway to cigarettes smoking were reported. There is agreement between Erku et al and the current survey that use in indoor public places, as well as advertisement and sales to minors should be forbidden. In Erku et al, most health-care professionals did not proactively recommend ENDS, but support its use in specific situations such as patients with comorbidities, unsuccessful quit attempts or patient preference. However, the review of Erku et al included only papers that were published before the EVALI outbreak which very likely may have changed healthcare professionals’ view on ENDS.

Use of ENDS remains debated worldwide and triggers passionate responses among experts in tobacco control and tobacco use disorder. Despite accumulating data, uncertainty exists about their benefit/risk ratio as a smoking cessation tool, and the frequent dual use lead to uncertainty about its regulatory and policy aspects. The EVALI epidemic in North-America and the potential association of its use with COVID-19 outcomes introduced further uncertainty about their safety.

The range of EC devices, their electric characteristics, the flavours, nicotine content of the liquids used, the
concentration of compounds in the aerosol, the bioavailability of components, the individual patterns of use are highly variable. For this reason, the survey considered ENDS in general.

An agreement was reached that HTP and ENDS represent a health risk for non-smokers and for smokers who quit more than 6 months ago despite the lack of medium-term or long-term safety data on ENDS or HTP. A smoker has an excess risk due to smoking. When he/she quit the residual risk due to previous smoking persists and is slowly decreasing. The agreement of responders means that ENDS/HTP use represents an additional risk (e.g., by the chronic inhalation of e-liquid vapour) for non-smokers, and for former smokers on top of the residual risk due to previous smoking. The emerging main issue is the global assessment of the benefit and safety of ENDS for smoking cessation compared with both continuing smoking and to quitting smoking with evidence-based smoking cessation interventions.

We used the 6-month cut-off because most smoking cessation clinical trials follow-up participants up to 6 months5;11, because the likelihood of relapse is higher during the first 6 months after stopping smoking than after 6 months12 and because data show that ENDS or HTP may also trigger relapse to smoking around this time.13 14

**Implications for clinicians, policy-makers and future research**

The current survey highlights issues that should be addressed in future research supported by clinicians and policy-makers. Sufficiently powered randomised placebo and reference intervention controlled clinical trials should assess the ENDS’ place among smoking cessation interventions.15 Longitudinal data should be collected to evaluate their long-term population efficacy and safety compared both to continuing tobacco use and long-term smoking abstinence. Further research may assess whether limiting the maximum nicotine concentration in e-liquids is justified and what is the range of nicotine content resulting in smoking cessation in large populations.

Alternative nicotine delivery systems are frequently described as a risk-reduction tool because they may deliver less toxic compounds than cigarettes. However, the notion of risk reduction implies measuring morbidity and mortality ratios in comparison with continuing tobacco use and complete tobacco and/or nicotine abstinence.

In this survey, consensus was reached that advertisement should not target minors, non-smokers or former smokers; use of ENDS should be forbidden in indoor public places; and health authorities should advise never-smokers not to use ENDS.

Well designed studies addressing specific issues and allowing firm conclusions are the best way forward.1 8 15 However, when uncertainty remains and clear-cut evidence is missing, collecting experts’ opinions and reaching a consensus is a way to reduce even modestly the level of uncertainty.3 4

**CONCLUSIONS**

A consensus was reached concerning ENDS: components of e-liquids should be provided on the product; an upper limit of nicotine concentration should be defined; a warning on the lack of evidence in long-term safety and the addiction potential should be stated. ENDS should not be regulated as consumer products but either as a new category of nicotine delivery or tobacco products; ENDS should not be sold in general stores but in specialised shops, shops selling tobacco or in pharmacies with restriction on sale to minors. Administration of illegal drugs is likely with ENDS. Concerning HTP products, a consensus occurred that HTP products have the same addictive potential as cigarettes; they should be regulated as a tobacco product with similar warning messages as cigarettes and their advertisement should not be allowed. The experts agreed that ENDS and HTP use should not be allowed in indoor public places and a specific tax should be implemented for ENDS; taxes on HTP should not be lower than those for conventional cigarettes. There was an agreement that the use of cigarettes is more likely with both ENDS and HTP (dual use) than quitting smoking.

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**ORCID iD** Ivan Berlin http://orcid.org/0000-0002-5928-5616

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