TOXICANT CONTENTS AND EMISSIONS IN SMOKELESS TOBACCO PRODUCTS (ARTICLE 9 AND 10, WHO FTC)

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Smokeless tobacco (ST) use is a global problem

Increased risk of:
- oral, esophageal and pancreatic cancers
- mortality from cardiovascular disease
- fetal toxicity

Total worldwide ST users = 302.4 million

NCI/CDC Smokeless Tobacco and Public Health: A Global Perspective, 2014
Differences in ST-related cancer risk across countries: oral cancer

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Country/region</th>
<th>Type of smokeless tobacco</th>
<th>Relative risk</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral cancer</td>
<td>India</td>
<td>ST without betel quid or areca nut</td>
<td>5.1 (4.3-6.0)</td>
<td>Boffetta et al. 2008</td>
</tr>
<tr>
<td></td>
<td>United States</td>
<td>Chew or snuff</td>
<td>2.6 (1.3-5.2)</td>
<td>Boffetta et al. 2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.7 (1.2-2.3)</td>
<td>Lee &amp; Hamling 2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3.3 (1.8-6.3)</td>
<td>Lee &amp; Hamling 2009</td>
</tr>
<tr>
<td></td>
<td>Scandinavia</td>
<td>Snus</td>
<td>1.0 (0.7-1.3)</td>
<td>Boffetta et al. 2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Snuff/Snus</td>
<td>1.0 (0.7-1.4)</td>
<td>Lee &amp; Hamling 2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.0 (0.7-1.5)</td>
<td>Lee &amp; Hamling 2009</td>
</tr>
</tbody>
</table>

\(^a\)Meta-analysis with smoking adjusted; \(^b\)Meta-analysis among ST users who were never smokers; \(^c\)Studies published since 1990 show no increase in oropharyngeal cancer risk
## Differences in ST-related cancer risk across countries: esophageal cancer

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Country/region</th>
<th>Type of smokeless tobacco</th>
<th>Relative risk</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal Cancer</td>
<td>India</td>
<td>Smokeless tobacco</td>
<td>3.7 (1.6-8.4)</td>
<td>Pednekar et al. 2011</td>
</tr>
<tr>
<td></td>
<td>United States</td>
<td>Smokeless tobacco</td>
<td>1.2 (0.1-13)</td>
<td>Boffetta et al. 2008</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chew or snuff</td>
<td>1.9 (0.8-4.2)</td>
<td>Lee &amp; Hamling 2009</td>
</tr>
<tr>
<td></td>
<td>Scandinavia</td>
<td>Snus</td>
<td>1.6 (1.1-2.4)</td>
<td>Boffetta et al. 2008</td>
</tr>
<tr>
<td></td>
<td>Scandinavia</td>
<td>Snuff/Snus</td>
<td>1.1 (0.9-1.3)</td>
<td>Lee &amp; Hamling 2009</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1.9 (1.0-3.7)</td>
<td>Lee &amp; Hamling 2009</td>
</tr>
</tbody>
</table>

*Meta-analysis with smoking adjusted; Meta-analysis among ST users who were never smokers*
Reason: Diversity of smokeless tobacco products and levels of harmful and potentially harmful constituents within and across countries
Variability of exposure to harmful constituents

Harmful Constituents

- Nicotine
- TSNA (e.g., NNN and NNK)
- PAH (e.g., benzo[a]pyrene)
- Metals (arsenic, cadmium)
- Volatile organic compounds (e.g., formaldehyde, acetaldehyde, crotonaldehyde)
- Micro-organisms

Stepanov et al., 2017
Constituents levels are related to exposure

Smokeless tobacco users (343)
Products with wide range of nicotine and TSNA levels

Multiple regression analysis for biomarkers levels (P-values)

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Urinary biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total nicotine equivalents</td>
</tr>
<tr>
<td>Constituent level in product</td>
<td>0.402</td>
</tr>
<tr>
<td>Tins per week</td>
<td>0.004</td>
</tr>
<tr>
<td>Total daily dip duration</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Dose-response relationship between exposure levels and cancer risk in smokers

Yuan et al., Carcinogenesis, 2011.
Factors that affect chemical composition of tobacco products

**Tobacco plant**
- Tobacco type
- Soil composition
- Fertilization
- Cultivation

**Product storage**
- Temperature
- Humidity
- Duration

**Tobacco processing methods**
- Bacteria control
- Curing
- Humidity

**Product formulation** (non-tobacco ingredients)
- Tonka beans
- Areca nut
- Alkaline agents
- Flavorants
WHO Recommendations under Heading of Reduce Toxicity

- Reduce the use of *Nicotiana rustica*
- Limit bacterial contamination, which can promote nitrosation and carcinogen formation (lowers nitrosamines)
- Require that tobacco be sun cured rather than fire-cured (lowers PAHs)
- Pasteurization to kill bacteria
- Improve storage conditions, such as refrigerating products before sale
- Affix a date of manufacture
- Eliminate ingredients such as areca nut and tonka bean which are known to be carcinogenic
Recommendations under Heading of Impose Product Standards

- Set upper limit of 2 μg/g (dry weight) for tobacco-specific nitrosamines NNN plus NNK

- Set upper limit of 5 ng/g (dry weight) for benzo[a]pyrene

- Monitor levels of arsenic, cadmium and lead in tobacco
Recommendations under Heading of Reduce Appeal and Addictiveness

- Reduce the appeal of and addiction to tobacco products [by] banning sweeteners and flavourings (including herbs, spices and flowers)

- Set limits on free nicotine and alkaline agents that increase pH

The time to act is now!