



Editorial

## The New Tobacco Companies Offensive: The Nicotine Pouches

Nicotine pouches (NPs) are oral administration bags containing nicotine salts together with other substances, including microcrystalline cellulose, sodium carbonate and other carbonic salts, citric acid, and various flavourings. Another method of nicotine consumption is the Swedish Snus (SS) that is a powdered tobacco product packaged in a pouch. The most important difference between them is that NPs do not contain any tobacco. For NPs the nicotine is extracted from the tobacco plant, processed and then added to the finished pouch product. Both, NPs and SS are placed between the upper lip and gum for up to 20–30 min, then removed.<sup>1</sup> The sale of SS is illegal in the European Union, except Sweden.<sup>2</sup> Conversely, NPs are unregulated products, so their sale is not prohibited in Spain (nor in the European Union) and they can be used virtually anywhere.

In a recent study,<sup>3</sup> whose objective was to analyse levels of constituents such as nicotine, and to screen for tobacco-specific nitrosamines (TSNAs) in 46 brand varieties of pouches with and without nicotine, they found that the average weight per pouch was 0.6 g and the nicotine content per pouch was 9.48 mg. The highest nicotine content was 47.5 mg per pouch and the lowest was 1.79 mg per pouch. Nicotine content was declared clearly on only about a third of the nicotine pouches examined, but most products described the nicotine strength, using either a scale or a figurative language.<sup>1</sup> Other studies have found similarly high concentrations of nicotine in NPs.<sup>1</sup>

NPs are highly addictive. Indeed, in a recent study<sup>4</sup> when authors examined the characteristics of those who use oral NPs and trends in use over time in a sample of US youth and young adults, they found that most of those who had ever used oral NPs continued to use it. In a study that aimed to compare the pharmacokinetic, pharmacodynamic, safety and tolerability profiles of two NPs with cigarettes, they found that NPs, like cigarettes, reduced subjects' urge to smoke and presented favourable product liking scores.<sup>5</sup> Another study,<sup>6</sup> demonstrate that NPs can provide nicotine in amounts sufficient to replicate cigarette smokers' nicotine uptake following a switch from conventional cigarettes to NPs products. Indeed, NPs can offer smokers a satisfactory, complete substitute for continued cigarette smoking. Patel et al.<sup>4</sup> have demonstrated that NPs could be a gate for smoking cigarettes. They found that 73% of those who currently used pouches and 33% of those who ever used pouches but not currently, reported current cigarette smoking. So, an appropriate regulation is needed so that nicotine-naïve individuals do not initiate use and those currently using tobacco do not use oral NPs concurrently with other products.

Nicotine is not only addictive but also toxic: nicotine exposure triggers a number of reactions in the body, depending on the dose: it causes an increase in blood pressure as well as an

increase in heart rate. Mild symptoms of intoxication include nausea and vomiting, with symptoms from higher levels of exposure including diarrhoea, increased salivation and a slowing of the heart rate. Severe poisoning can be characterised by seizures and respiratory depression.<sup>1</sup> In recent years, there have been numerous published cases of poisonings involving NPs.<sup>1,7</sup> Moreover, there are concerns for young people and other vulnerable groups (pregnant, breastfeeding women and people with cardiovascular diseases) given the addictive potential of nicotine and its strong effects on the cardiovascular system.<sup>1</sup> NPs are marketed as “tobacco-free” and may include claims that they are potentially safer than smoking, but it is known that the use of NPs is not free from harmful effects on health.<sup>1</sup> A recent review including both industry and non-industry funded studies<sup>8</sup> found that, in terms of toxicity, 186 different chemical components that are present besides nicotine, with an average of 17 constituents in each NPs. Eight were classified as hazardous according to the European Classification Labelling and Packaging Regulation, and methyl eugenol, benzophenone, and  $\beta$ -myrcene were classified as possibly carcinogenic to humans by the International Agency for Research on Cancer. Among other carcinogens, tobacco-specific nitrosamines (TSNAs, genotoxic carcinogens), were detected in 26 of the 44 NPs samples from 20 manufacturers. The authors report that the highest detected levels were lower than those typically found in cigarettes and SS, but they are found in sufficient quantity to do harm.<sup>8</sup> NPs do not contain any tobacco; the added nicotine may have been obtained by extracting tobacco leaves and thus may contain trace amounts of TSNAs.<sup>1</sup> In another study authors found that TSNAs were detected in more than half of the NPs analysed and the highest concentrations found were 13 ng per pouch for N'-nitrosonornicotine (NNN), 5.4 ng per pouch for 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 2.5 ng per pouch for N'-nitrosoanatabine (NAT) and 5.6 ng per pouch for N'-nitrosoanabasine (NAB).<sup>3</sup> On the other hand, in some plant-based NPs samples, levels of acetaldehyde, nitrite, and nickel were substantially higher than in SS products.<sup>8</sup> When analysing in vitro toxicity using data from non-industry-sponsored studies, results show that comparative analyses of inflammatory response, reactive oxygen species (ROS) production, and cytotoxicity between identical flavours of four various nicotine strengths of major NPs brands found increased cytotoxicity, differential ROS, and pro-inflammatory cytokine release in human bronchial epithelial cells compared to untreated cells at lowest concentration treatments at 4–24 h.<sup>8</sup> In human oral gingival epithelial cells, increased cytotoxicity, differential ROS, and cytokine release were observed in NPs at the highest nicotine concentration and besides, NPs were found to induce an oxidative stress response in human gingival fibroblasts

<https://doi.org/10.1016/j.arbres.2024.10.017>

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after 24 h of exposure.<sup>8</sup> Rungraungrayabkul et al.,<sup>9</sup> found that oral mucosal changes at the site of placement were common among NPs users. Indeed, lesions varied from slight wrinkling, dry mouth, soreness, gingival blisters, a strange jaw sensation and various white lesions associated with elevated levels of inflammatory biomarkers such as IL-6, IL-8, IL-1 beta, and TNF-alpha, suggesting a potential risk of oral cancer.<sup>10</sup> Several studies have shown that nicotine promotes conditions such as gingivitis, periodontal disease, and bone destruction, supporting the hypothesis that NPs may induce inflammation in periodontal tissue.<sup>9</sup>

NPs manufacturers are employing a wide range of marketing strategies across multiple channels, including online media, sports sponsorships, and out-of-home advertising. Many of these advertising strategies closely resemble those historically used by the industry to promote other nicotine and tobacco products like e-cigarettes.<sup>11,12</sup> Evidence suggests that the advertising is targeted at non-smokers and younger people, which could lead to new nicotine addictions.<sup>11</sup> The tobacco industry focuses its advertising on harm reduction.<sup>13</sup> There is a need for thorough control of advertising and marketing and, above all, clear regulation of this product.

We express our deep concern about the growing popularity of these NPs, which we consider a major risk to public health, especially for young people. The high content of nicotine and other toxic substances, their proven addictive capacity, the evidence that points to them as causing toxicity and being harmful for human tissues, their capacity as a gateway to tobacco consumption and the use of advertising campaigns similar to those historically used by tobacco companies suggest that these products should be prohibited or, at least, strictly regulated.

## Conflicts of Interest

JIG-O has received honoraria for lecturing, scientific advice, participation in clinical studies or writing for publications for the following (alphabetical order): Adamed, Aflofarm, Boehringer Ingelheim, Neuraxpharm and Pfizer. CAJR has received honoraria for presentations, participation in clinical studies and consultancy from: Adamed, Aflofarm, GEBRO, GSK, Kenvue, Menarini, Neuraxpharm and Pfizer. MG is the country coordinator of SOLACE (an EU co-funded study on lung cancer screening) and have a travel grant from Menarini.

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