

Nitrosamines in modern Western smokeless tobacco:  
The scientific evidence does not support the claim that different levels between  
U.S. and Swedish products cause different health effects.

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I am an Associate Professor at the University of Alberta School of Public Health, where I research and teach epidemiology and health policy, and direct the Alberta Smokeless Tobacco Research and Education Group. I am also editor-in-chief of the academic journal, *Epidemiologic Perspectives & Innovations*. I have been asked by U.S. Smokeless Tobacco Company to evaluate claims that different levels of nitrosamines in modern Swedish- and U.S.-manufactured smokeless tobacco products are responsible for a difference among the health effects of those products.

Modern Western smokeless tobacco (ST) products include currently-manufactured Western moist snuff (the Swedish word for such products is *snus*) and chewing tobacco (except where otherwise noted, these are the products referred to in this report). I have made an extensive study of the published health research about smokeless tobacco. Based on that evidence and on my expertise in health science, my conclusions are the following:

1. There is no evidence that modern ST products from Sweden and from the U.S. differ in their health effects.
2. Tobacco-specific nitrosamine (TSNA) levels have dropped substantially in both U.S. and Swedish products over the last three decades. The epidemiologic evidence shows that older products, which had higher levels of TSNA than current U.S. or Swedish ST, caused no measurable health effects. Thus, if TSNA in ST do cause disease, current products would cause even lower levels of disease than products that caused no detectable level of disease.
3. There is no evidence that nitrosamines, as a constituent of ST, cause cancer or any other disease in humans.

These points are detailed below.

#### Background

Overwhelming evidence shows that any risk of life-threatening disease from the use of ST is very small. Indeed, there is no definitive evidence that ST causes any life-threatening disease. This does not mean that there is zero mortality risk from ST, since it is always impossible to detect the

difference between a very low risk and zero risk. But the evidence does show that any risk of life-threatening disease is very low, and in particular, is much lower than the risk from smoking. The best estimates put the risks from ST in the order of 1/100th that from smoking.

Since ST provides nicotine in amounts and at rates similar to that from smoking, the different health risks mean that ST is promising as a harm-reducing alternative to smoking. As tobacco harm reduction has been increasingly discussed, claims have been made that U.S. ST products do not reduce harm as much as Swedish products, in part because the latter have lower TSNA levels. However, there is no scientific evidence to support this conclusion, and the evidence shows that to the extent that there is a difference, it is tiny.

#### Background on the epidemiologic evidence about ST

Epidemiology is the study of actual diseases in actual people. It differs from other health sciences, which can merely suggest that an exposure might cause a disease, because it directly studies and measures such effects. Thus, when we have epidemiologic evidence, the suggestive evidence from other sciences is of limited value. There is ample epidemiologic evidence about ST.

Epidemiologic results are often misinterpreted as dichotomous, such that a result may suggest there is a measurable association between an exposure and a disease, but if no association is found, the study is labeled uninformative. But epidemiologic data can also actively support the conclusion that there is no (or very little) association between an exposure and a disease. In the case of cancer risk from ST, the evidence supports this latter conclusion. This is true for both modern U.S. and Swedish products. Clearly, since any effects are too small to measure, any difference in effects among products must be smaller still. Claims of effects that are too small to measure are obviously pure speculation. Furthermore, the evidence shows that ST products with TSNA levels higher than current products caused no measurable increase in life-threatening disease, as presented in detail below.

To fully appreciate these points, it is necessary to briefly review the chemistry and related sciences.

#### Nitrosamines and toxicology

Nitrosamines are a group of chemicals people are exposed to via food, tobacco products, and other pathways, and some nitrosamines (for some doses and for some exposure pathways) have been shown to be carcinogens. The caveats in the parentheses are necessary because there is a truism in toxicology that "the dose makes the poison," or more precisely, the dose plus the pathway makes the poison. At the right levels and delivered in the right form, any chemical can be safe, while for other doses and pathways, the same chemical will be deadly.

In the context of ST, discussions of nitrosamines focus on the TSNA's. Studies that inflicted exposure of these chemicals on non-human animals have shown that they can cause some types of cancer, in certain doses, when delivered in certain ways. Studies that actually used oral

exposure to ST in non-human animals have generally not found carcinogenicity (Grasso and Mann, 1998).

The nature of toxicology is that if you try enough different exposures, and enough times, it is inevitable that an elevated disease rate will be observed, even if by chance alone. Thus, having a few suggestive toxicologic results is not informative. But even if the evidence showed definitively that ST causes cancer in non-human animals under certain circumstances, this would merely be *suggestive* of a human health effect. The exact exposure pathway matters, and it is well documented that many exposures are carcinogenic in one animal but not others. What we really care about is whether the actual exposure that people experience causes human disease. In the absence of any direct observations of human health effects, toxicologic evidence might be better than nothing, and provide a reason to suspect there *might* be a measurable human health effect. But we have those direct observations (the epidemiology), and they show there is no measurable health effect. It makes no sense to appeal to indirect suggestive evidence that something is a *potential* health hazard when it actually *has been shown* to not be a substantial health hazard.

#### Levels of TSNAs in ST

A possible response to this is that the majority of the useful epidemiology about ST is from Sweden, and Swedish products have lower levels of TSNAs than U.S. products. Thus, the argument might go, the U.S. products might have larger health effects. This argument might seem valid on its face, but it is easy to see that it is incorrect. To show that, it is useful to first briefly review the literature on the concentration of TSNAs in ST products.

While it appears that at any point in time, the TSNA levels of Swedish ST have been lower than those of U.S. ST, it is more important to note that the levels have dropped dramatically in all of these products. Much has been made of the change in the Swedish production process that took place in the early 1980s, switching from fermented products to non-fermented, which reduced TSNA levels. Published measures of TSNAs in ST have shown a substantial reduction over 25 years, but this is true for both Swedish and U.S. products (Rodu and Jansson 2004; Ramstrom 2000; Osterdahl, Jansson, and Paccou 2004, Hoffmann et al. 1995; Djordjevic, Brunnemann, and Hoffmann 1993). In particular, the published research supports a claim that all current products have levels of TSNAs that are at least as low as any product had 25 years ago. Rodu and Jansson (2004) provide a comprehensive summary of 14 published results that demonstrates that trend. This observation is crucial, as shown below.

Precisely quantifying the levels of TSNAs is difficult, because different studies measure different chemicals, there is some confusion about units (particularly whether the measure is the proportion of wet or dry weight), and most important, natural variation among different samples of the product. There is inevitably also some measurement error. As a result, it is not possible to precisely measure how much levels have decreased, and published measurements of TSNA quantities differ substantially. (Nevertheless, some authors have ventured fairly precise claims about the decrease. For example Hoffmann et al. (1995) concluded that levels in U.S. snuff

dropped by more than 70% between 1980 and 1995.) Fortunately, such precise measurements are not necessary.

#### The Swedish epidemiology applies equally to the U.S. products

Claims that the U.S. and Swedish products have different health effects seem to be based largely on studies of oral cancer (OC) – one U.S. study in particular. Studies of other cancer sites or all-site cancers even more strongly support a null or near-null association, and these results are consistent across U.S. and Swedish studies. Studies of cancer other than OC lack even the one positive association from a large study that exists for OC. (That one result appears to be largely responsible for the belief that OC is associated with ST, and for the suggestion that U.S. and Swedish products differ.) Thus, any claims about different health effects seem to be based entirely on OC.

The two largest studies of ST and OC from Sweden (Schildt et al. 1998; Lewin et al. 1998) failed to find a measurable association and provide strong evidence against there being any substantial association. One large U.S. study (Winn et al. 1981) showed a positive association that has never been replicated. (Results from about 30 other studies with smaller effective sample size show roughly the distribution around the null we would expect based on the Schildt and Lewin results.) Some observers have suggested that the contrast among the three larger studies reflects a difference in risk from U.S. and Swedish products. But this ignores several easily-observed points.

First, the older Swedish products used by the Schildt and Lewin populations were mostly pre-reformulation (fermented) products, which are believed to have had higher levels of TSNAs than current U.S. or Swedish products (Ramstrom 2000). Thus, if TSNAs in ST are indeed a carcinogen at some level (a claim which there is no actual evidence to support, but which can be assumed for the sake of argument), then current U.S. products and current Swedish products cause even less risk than products that have already been shown to cause no measurable risk. Consider the details of those two important studies:

-Schildt et al. (1998) studied individuals diagnosed with OC during 1980-89, who averaged about 70 years of age, finding no measurable association of OC and ST use. Most, or perhaps all, of their subjects who used ST must have used the pre-reformulation fermented product, with its higher level of TSNAs, for most of the time they used ST – some for many decades. Some of them (those who were diagnosed at the beginning of the recruitment period) had never used anything else. Thus, the vast majority of – and possibly all of – the exposure was during a period when Swedish products had higher TSNA content than current U.S. or Swedish products.

-Lewin et al. (1998) collected OC cases from 1988 through early 1991, and also found the association with ST use was very small or null. Current users of ST among these subjects would have been using reformulated products for the years immediately prior to diagnosis, though the products still may have contained as much TSNAs as current products from the U.S. (the limited publicly available data makes it difficult to be certain). However, 31 of 83 exposed cases had

used ST for at least 30 years, so were exposed to pre-reformulation product for at least 20 years, and many of the others had likely been using ST for ten years or more. Those who had used for 30 years had OC risk the same as shorter-term users or non-users.

In addition, a more recent Swedish study by Rosenquist et al. (2005) explicitly compared the outcomes of subjects exposed to fermented (pre-reformulation) products and those exposed exclusively to non-fermented products. This is the first study that has been able to make such a comparison, since all or nearly all subjects in all previously published studies were exposed to fermented products. They collected OC cases from 2000 to 2004, and found no evidence of an association with ST. They explicitly analyzed the years that subjects were exposed to fermented products, finding that three-quarters of those exposed had been exposed to fermented products and that exposure, like the exposure to exclusively non-fermented products, was not associated with OC.

Thus, it is clear that even if products with high enough levels of nitrosamines might cause cancer, products with greater than the current levels (in U.S. or Swedish products) have been repeatedly shown to not do so at any measurable level.

#### U.S. studies also provide evidence against the claim there is a difference

Moreover, the evidence about older U.S. products generally fails to show an association with cancer. The Winn study is an outlier (though even its result is not as strong as the rhetoric sometimes suggests), and there are always a lot of possible explanations for an outlier result. It is likely that the product used by that population had much higher TSNA levels than any current ST, which might mean that it was more carcinogenic, though this is purely speculative. But there were also other differences between the product and modern ST, and the study was of an unusual population with an unusual exposure pattern. Thus, any number of real differences – as well as various forms of study error and the way the data was analyzed and presented – could explain the unusual result. None of these hypotheses about the result suggest there is a nationality difference between modern products.

Setting aside this one study, studies from the U.S. do not demonstrate an association between the studied U.S. products (which presumably had higher TSNA levels than present products) and OC. This is further evidence against the claim that there is a difference among the products. In science, when we have one result that contradicts the clear conclusion from the rest of the data, we have to trust the rest of the data, not the odd result.

Some observers may have concluded that because the best evidence that the risk is very low is from Sweden, it must be that the risk is higher in the U.S. But the difference in the amounts of evidence is a result of available data, not apparent differences. We have a larger number of convincing results from Sweden because there is a difference in exposure prevalence. It is very difficult to study the relationship of an exposure and a rare disease, like OC, in a population where the exposure is also rare (as ST is in the U.S.). Thus, we would expect (and do indeed have) more definitive results from Sweden, a country with generally better data on population

health and a higher prevalence of ST use. Nevertheless, the Winn study is not the only U.S. evidence, and the body of U.S. evidence still suggests a very low level of risk.

It is important to understand that for any set of studies that contains one relatively large study with a large positive outlier result, if the studies are divided into two groups, then one of them has to contain the outlier. That group will then probably show a larger average association. This is true no matter the reason for the outlier result (e.g., study error, unusual exposure) and no matter what method is used to categorize the studies (e.g., by nationality, by the year the study was done). Thus, the fact that when studies are divided by nationality, the average association for the U.S. studies is higher, pulled up by the Winn result, cannot be seen as telling us anything about nationality differences.

### Conclusions

In sum, whatever the toxicology about carcinogenicity of TSNAs (in some form and dosage, in some animals), the epidemiology trumps any conjecture that the TSNAs in ST cause a measurable level of cancer in humans. Both the Swedish epidemiology, based on exposure to older products, and the U.S. epidemiology have looked at the effects of products with TSNA levels at least as high as current U.S. products, and have not found a measurable association with cancer, let alone a different association across nationalities. Claims that there are different risks between U.S. and Swedish products are mere speculation.

There is no evidence of differences in health risks among modern Western ST products, and no evidence that even lower levels of TSNAs would reduce the already unmeasurably-small risks. But the differences between ST and smoking are huge. The costs of delaying the introduction of ST because of debates and speculation about tiny differences in risks far outweigh any imaginable benefit from a hypothetical slight reduction in risks from ST. Every day that these products are not available is a day that people keep smoking rather than switching.

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