Smokeless Tobacco – An Overview*

by

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SUMMARY

Smoking, especially cigarette smoking, is the most common form of tobacco consumption world-wide. It is generally accepted that smoking carries health risks for smokers. The combustion and pyrolysis products of tobacco generated during smoking are considered to be responsible for the harmful effects. Smokeless tobacco, another wide-spread form of tobacco use, is not subjected to burning and produces no combustion or pyrolysis products. Therefore, there is an increasingly intense debate about the potential role of smokeless tobacco in reducing the harm of tobacco use.

An overview is presented on the different types of smokeless tobaccos consumed around the world. Commercial products differ widely in composition and patterns of use. The smokeless tobaccos of the Western world (Europe and North America) need to be clearly distinguished from those popular in Asia, Africa and South America. The modern smokeless tobaccos used in Europe and North America are reviewed regarding their chemical composition and toxicological properties. Agents of concern found in smokeless tobacco, especially the tobacco specific *N*-nitrosamines, are dealt with in particular.

The epidemiological evidence is summarized concerning a wide range of health outcomes. Published reviews and studies are presented and interpreted regarding non-neoplastic oral diseases, various forms of cancer, circulatory diseases, several other diseases and pregnancy outcome. While many of the epidemiological studies have weaknesses and data are often inconsistent it is quite obvious that smokeless tobacco use is much less risky for consumers than smoking. In fact, for modern forms of European moist snuff such as Swedish snus, which is subject to strict quality standards, there is evidence for – if any – only very limited serious health risk.

The ongoing public discussion centers around the influence smokeless tobacco may have on smoking rates (initiation or cessation) and the occurrence of tobacco specific diseases - with Sweden being a revealing example. There is an interesting controversy regarding product and marketing regulations for smokeless tobaccos in the European Union. [Beitr. Tabakforsch. Int. 223 (2009) 248–276]

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ZUSAMMENFASSUNG

Rauchen – vor allem von Zigaretten – ist weltweit die üblichste Form, Tabak zu konsumieren. Es ist allgemein anerkannt, dass Rauchen gesundheitsschädlich ist. Die Verbrennungs- und Pyrolyseprodukte, die beim Rauchen des Tabaks entstehen, werden für die schädlichen Wirkungen verantwortlich gemacht. „Smokeless tobacco", eine andere weit verbreitete Form des Tabakgenusses, wird dagegen nicht verbrannt und bildet keine Verbrennungs- oder Pyrolyseprodukte. Daraus hat sich eine Debatte steigender Intensität ergeben über die Rolle, die „smokeless tobacco" bei der Verminderung tabakbedingter Schäden spielen könnte.
In einem Überblick werden die verschiedenen weltweit konsumierten Formen von „smokeless tobacco" vorgestellt. Die Handelsprodukte unterscheiden sich erheblich in ihrer Zusammensetzung und ihrem Gebrauch. „Smokeless tobacco" in der westlichen Welt (Europa und Nordamerika) ist klar von dem zu unterscheiden, der in Asien, Afrika und Südamerika verbreitet ist. Die chemische Zusammensetzung und die toxikologischen Eigenschaften von modernem „smokeless tobacco" in Europa und Nordamerika werden besprochen. Die Betonung liegt dabei auf den problematischen Bestandteilen in „smokeless tobacco", besonders auf den tabakspezifischen *N*-Nitrosaminen.
Die epidemiologischen Befunde für ein weites Feldes gesundheitlicher Auswirkungen werden zusammengefasst. Publizierte Übersichtsartikel und Studien werden vorgestellt und interpretiert betreffend nicht-neoplastische orale Krankheiten, verschiedene Formen von Krebs, Krankheiten des Kreislaufs, bestimmte andere Krankheiten und Schwangerschaften. Obwohl zahlreiche epidemiologische Studien Schwächen aufweisen und die Daten oft widersprüchlich sind, ist es ziemlich offensichtlich, dass der Genuss von „smokeless tobacco" für den Konsumenten viel weniger Risiko birgt als das Rauchen. Für die heutigen Formen von europäischem „moist snuff" wie dem schwedischem „snus", der strengen Qualitätsstandards unterworfen ist, hat sich in der Tat – wenn überhaupt – nur ein sehr begrenztes Risiko ernster gesundheitlicher Folgen gezeigt.
Die öffentliche Diskussion betrifft den Einfluss von „smokeless tobacco" auf den Anstoß zu rauchen oder es aufzugeben und auf das Auftreten tabakbedingter Krankheiten, wobei Schweden als aufschlussreiches Beispiel dient. Eine interessante Kontroverse betrifft die Produkt- und Marktregulierungen für smokeless tobacco in der Europäischen Union. [Beitr. Tabakforsch. Int. 23 (2009) 248–276]

RESUME

Le fumage – particulièrement le fumage de cigarettes – constitue le moyen le plus courant de consommation du tabac dans le monde entier. Il est généralement admis que le fumage entraîne des risques pour la santé. Les produits de combustions et de pyrolyse du tabac générés au cours du fumage sont considérés comme être responsables des effets nuisibles. Les produits de tabac sans fumée (à macher ou à priser), ce qui constitue un autre moyen très répandu de la consommation du tabac, ne sont ni brûles ni pyrolysés. Par conséquent, il existe un débat de plus en plus intense sur le rôle potentiel que jouent des produits de tabac sans fumée pour la réduction des effets nuisibles de la consommation du tabac.
Un bref aperçu est donné sur les différents types de tabacs sans fumée consommés dans le monde entier. Les produits disponibles sur le marché sont fortement différents dans la composition et les modes d'utilisation. Les produits sans fumée disponibles en Europe et l'Amérique du Nord sont clairement à distingués des produits vendus en Asie, en Afrique et en Amérique du sud. Les tabacs sans fumée consommés en Europe et en Amérique du Nord sont examinés ici concernant leur composition chimique et leurs effets toxicologiques. Les composants d'intérêt particulier, présent dans le tabac sans fumée, particulièrement les *N*-nitrosamines spécifiques du tabac (TSNA) sont examinés plus en détail.
Un résumé sur l'évidence épidémiologique des effets sanitaires allégués du tabac sans fumée est présenté. Un aperçu de la littérature est donné et examiné concernant les maladies de la bouche non néoplastiques, les différentes formes du cancer, les maladies du système circulatoire, plusieurs autres maladies et la grossesse. Alors que beaucoup des études épidémiologiques souffrent de faiblesses et de données contradictoires, il semble être évident que la consommation du tabac sans fumée est moins nuisible à la santé que le fumage. En effet, pour les marques commerciales modernes européennes de tabac à sucer, comme le tabac à sucer suédois, soumis à des normes strictes de qualité, des données suggèrent que les risques sanitaires soient, s'il y en a, très réduits.
Les discussions en cours traitent de l'influence potentielle du tabac sans fumée sur le comportement de fumage (commencement ou cessation) et des maladies spécifiques du tabac, la Suède servant comme un exemple. Une controverse intéressante est en cours dans l'Union européenne concernant la législation commerciale relative au tabac sans fumée. [Beitr. Tabakforsch. Int. 23 (2009) 248–276]

INTRODUCTION

Smoking, especially cigarette smoking, is the most common form of tobacco consumption world-wide. It is generally accepted that tobacco smoking carries health risks for smokers, such as different forms of cancer and diseases of the heart and circulatory system (1). Certain combustion and pyrolysis products of tobacco generated primarily during puffing, such as polycyclic aromatic hydrocarbons, phenols, carbon monoxide, nitric oxide, acetaldehyde, isoprene and butadiene, are considered to play a key role in increasing the health risks for smokers. In addition, several biologically active endogenous tobacco constituents are directly transferred from tobacco into smoke, such as nicotine, the tobacco specific *N*-nitrosamines and aroma substances (2).
Besides smoking, tobacco may also be consumed without burning in form of the different kinds of "smokeless tobacco". Smokeless tobaccos do not give rise to substances usually generated by tobacco burning. Therefore, smokeless tobacco use may be seen as a "less harmful" alternative of tobacco consumption compared to smoking.

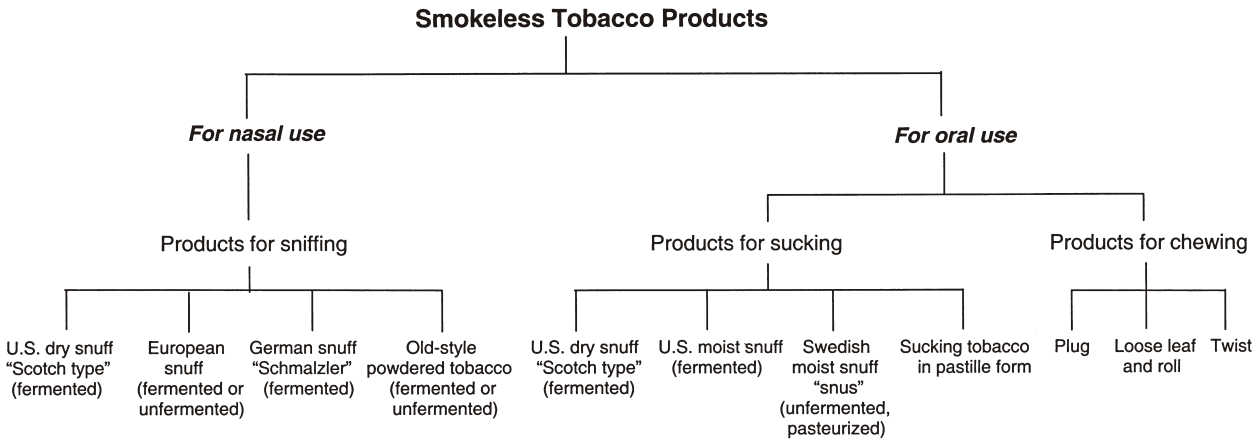

Figure 1. Smokeless tobacco products consumed in Europe and the USA. In Europe including Great Britain, "snuff" is used to denote sniffing tobacco while in the USA this word is the term for oral tobacco; U.S. dry snuff may be consumed by sniffing or sucking.

There are different kinds of smokeless tobacco, generally divided into nasally and orally used products. They are subdivided into several types with distinctive properties and presumably different toxicity and carcinogenic potential (3, 4). The large number of different smokeless tobacco types may be confusing for scientists, regulators and politicians. This is especially true for the various kinds of snuff. The smokeless tobaccos used world-wide differ in composition, manufacturing processes, the way they are consumed and, consequently, their physiological effects and toxicity. In addition, certain products, in particular the various forms of snuff, have undergone profound product modifications in the last decades. For these reasons, "smokeless tobacco" cannot be regarded and classified as a homogeneous material. Consequently, it is mandatory to differentiate and to know precisely which product manufactured at which time was investigated regarding its composition, toxicity and health effects.
To start with, an overview on smokeless tobacco, especially the types consumed in Europe and the USA, is presented in this paper together with brief information concerning smokeless tobacco products used in other areas of the world. This is intended to form the basis for describing and characterizing – as precisely as possible – the products for which data are reviewed and discussed in this paper.

1 DESCRIPTION OF SMOKELESS TOBACCOS – SMOKELESS TOBACCOS IN EUROPE AND THE USA

Figure 1 shows a diagram of the smokeless tobacco products consumed predominately in Europe and the USA.

1.1 *Tobacco products for sniffing*

This form of smokeless tobacco is exclusively consumed in small pinches through the nose. Nicotine is absorbed via the nasal mucosa.
The tobacco blends of nasal snuff commonly consumed in central Europe consist of tobaccos of various origins and different varieties, such as Virginia and Oriental tobaccos. After fine milling the tobacco powder is subjected to fermentation in the presence of an aqueous sodium chloride solution. A wide variety of aroma substances and essential oils may be added as make-up to finish the snuff. With around 20% water content this product is relatively humid. Nasal consumption requires pinches of approximately 30 to 50 mg. After a short time the tobacco is removed by blowing one´s nose.
The use of nasal snuff is widespread in Central Europe among men and especially persons working in occupations were smoking is not allowed, e.g., underground miners. Snuff stimulates nasal secretion and, consequently, the mucous membranes are kept moist. This results in less inhalation of stone or coal dust because the dust particles are retained by the moist nasal membranes (5).
The classical German nasal snuff, "Schmalzler", is manufactured only in Bavaria. It is a black-brown, granular snuff consisting of Brazil tobaccos, as used in cigars, as well as dark, heavy-bodied, aromatic Brazil tobaccos, so-called mangotes. After a special kind of fermentation followed by gentle and slow milling, paraffin oil and several aroma substances are added – depending on the recipe of the specific brand. In the past, molten butter was the specific ingredient used in this form of snuff. The German word "Schmalz" means molten butter and is the origin of the name "Schmalzler". The addition of molten butter to tobacco resulted in less dusty pinches, which were preferred by the consumers. Today´s addition of paraffin oil shows a comparable effect. This kind of snuff is offered to consumers with a water content of about 12% and used in relatively large pinches of about 0.1 g. Consumers are predominately older males living in Bavaria (5).
Old-style powered snuff is similar to the type of nasal snuff, which has been consumed in Europe since the fifteenth century. The production methods vary considerably. A specific snuff, its composition and method of production in the eighteenth century, is described by S. KOZLOWSKI (6). Today, this kind of snuff has a negligible market share in Europe, only a few fringe market products are still available.
U.S. dry snuff consists mainly of fermented fire-cured tobaccos and is offered to consumers in powder form with a moisture level between 4 and 6%. Originally, this form of snuff was ingested by nasal inhalation. Under the name "Scotch snuff" its use is common today.

Due to the way of curing and fermentation some of these tobaccos contain high amounts of tobacco specific *N*-nitrosamines (TSNAs) (7). Fire cured tobaccos are responsible for traces of polycyclic aromatic hydrocarbons (PAHs) in the blend (8).

1.2 *Tobaccos products for sucking*

Tobacco products for sucking are U.S. "dry snuff", U.S. "moist snuff", "Swedish snus" and sucking tobaccos in pastille form.

Since about 1800, U.S dry snuff has been consumed orally predominately by women in the Southern parts of the United States (9, 10). Its market share has declined by more than 70% between 1986 and 2005. Today, it is only of minor importance (11).

U.S. moist snuff, also called dipping tobacco, consists of cut air-cured and fire-cured tobaccos. The fermented, blended tobaccos are processed into fine particles (fine-cut) or strips (long-cut). Its water content is rather high (50–60%). Resulting from the curing and fermentation processes moist snuffs may contain relatively high levels of nitrite and, therefore, also of TSNAs. Traditionally, moist snuff is consumed in small portions, called "pinches", placed into the mouth between the gingival and buccal mucosa. Modern moist snuff products are offered in small pre-portioned sachets similar to tea bags. Positioned in the lower part of the mouth, these sachets remain in place. Consumption requires expectoration from time to time. Moist snuff is manufactured with different kinds of aromatic additives, such as wintergreen oil, spearmint, apple, cherry, vanilla, etc. Today, it is the most popular sucking tobacco in the United States; its sales have more than doubled between 1986 and 2005 (11).

The tobaccos used for Swedish "snus", a special type of moist snuff with a water content of around 50%, are primarily air-cured burley and sun-cured Oriental tobaccos not subjected to any fermentation. In snus manufacturing various brand-specific additives and aroma substances are used. Swedish snus is "pasteurized" by a gentle form of heat treatment and virtually sterile. Swedish snus is practically free of microorganisms and, as a result, the risk of nitrite formation from nitrate and TSNA formation is reduced (12, 13). The practice of refrigerating Swedish Snus at the outlet until sale is assumed to help keeping TSNA levels low over time (12).

It is manufacturer policy that Swedish snus products comply with the Gothia Tek Standard – a voluntary standard of Swedish Match, which regulates production procedures, the maximum levels of undesired substances in the finished product and Company information policy (12). Swedish snus is offered on the market in two different forms, as "lös snus" and "portion snus". "Lös snus" is a loose moist powder, packaged in containers usually made from cardboard, and needs to be portioned before consumption, either with the fingers or with special tools, e.g., a "prismaster". Portion snus is pre-packaged tobacco powder in small celluloses bags, which are put on the market in three different sizes (mini, normal and large).

Swedish Snus is consumed by placing it between the upper lips and the gums. This way, there is no need for expectoration. More than 50% of male Swedish tobacco consumers are snus users (14). Its consumption is increasing also in the USA (11).

Sucking tobacco in pastille form was recently offered in the USA as a new tobacco product. It consists of about 60% compressed fine-ground tobaccos and inorganic salts and is flavored with eucalyptus or mint. The nicotine up-take from a pastille is comparable to smoking a cigarette (15, 16).

1.3 *Chewing tobaccos*

Chewing tobaccos exist in different forms, such as plug, loose leaf and twist or roll.

Plugs were originally made by "plugging", i.e. placing fine-ground tobaccos soaked in wild honey into green hickory or maple hogsheads. After this casing procedure, the tobacco was pressed by machines into large blocks, which were – after a storage period – cut into smaller blocks, bars or plugs. Mild burley and Virginia tobaccos and typical tobaccos from the Philippines are used for manufacturing this kind of smokeless tobacco. "Moist plug" tobaccos have a moisture content of more than 15 %, "firm plug" tobaccos of less than 15%. In the past, plugs were the most important type of chewing tobacco in the USA; today they are of minor importance (11).

Loose leaf chewing tobaccos are primarily manufactured from air-cured tobaccos grown in Pennsylvania and Wisconsin. The tobaccos are shredded into flakes and cased with sweet, aromatic sauces. This type of chewing tobacco was consumed in the USA primarily by men living in rural areas. Its market share has been steadily declining during the last century (11).

Twist and roll chewing tobaccos are the typical forms of traditional European chewing tobaccos, especially in central and Northern Europe. Today, their consumption is no longer widespread. Twist chewing tobaccos consist of rolled leaves, which are plaited into a rope. The rope may also be made of spun tobacco, which is sometimes twisted, with diameters of 2.5 to 12.5 mm. This kind of chewing tobacco is made from generously cased heavy-bodied U.S. tobaccos, such as Kentucky or special burley tobaccos, as well as from Hungarian or German varieties. Roll chewing tobaccos often consist of an inner core or filler covered with a suitable tobacco seal as wrapper. In the past, this kind of tobacco was also smoked in pipes or consumed by nasal use. Twist tobacco is the only form of smokeless tobacco fashioned by hand.

2. DESCRIPTION OF SMOKELESS TOBACCOS – SMOKELESS TOBACCOS OUTSIDE EUROPE AND THE USA

Smokeless tobaccos are used by many cultures outside Europe and the USA, including India, Africa and South America. These products differ considerably from those consumed in Europe and the USA (7). A few of them are briefly described in this chapter for reasons of completeness and for advising against any inappropriate jumble of analytical, toxicological or epidemiological data.

"Paste", a special type of oral smokeless tobacco product, is traditionally used in Asia. The product consists of a tobacco paste, to which additional ingredients may be added. Its final moisture content is typically greater than

15%. For use, paste is placed between the lip and gum or cheek and gum.
In India, tobaccos for chewing are combined with betel leaf and sliced areca nuts, sometimes with powered slaked lime. Therefore, their toxicity and physiological effects are quite different from the European and U.S. smokeless tobacco products.
"Zarda", a special type of Indian smokeless tobacco, consists of partially fermented tobacco leaves, cooked in small pieces in water together with vegetable dyes. Perfumes are added for producing a scented tobacco which is either chewed alone or together with betel quid (17).
"Guthka" and "Kahini" are sweet "ready-to-eat" chewing tobaccos consisting of chopped tobacco containing betel leaf, catechu, saffron or slaked lime (18).
"Nas" is a form of powdered tobacco, which is also used for medicinal purposes, most frequently in the Himalayan region, Tibet and Mongolia. In addition, it is consumed for hedonistic and shamanistic purposes. For nas production tobacco is mixed with additives such as hellebore, other herbs and spices, ash and lime (19).
In Cambodia, tobacco is sniffed, often with lime, or chewed with betel (19).
In Africa, tobacco is smoked, sniffed, chewed, eaten and drunk as an extract. Tobacco is utilized for pleasure, as a magical plant, a burial offering, an object of barter and trade and as a status symbol. It is also used as medicine, insecticide and an additive for hunting poisons.
Snuff in Africa is often mixed with alkaline substances such as vegetable ash or potash, salt from salt lakes, oil, beef fat or powered fruits. For example, the use of snuff containing plant ash is a universal habit among the South African Bantu tribes. For preparing the vegetable ash, there are more than twenty herbs in common use, the favorite being aloe. After burning the dried plants, the ash is milled and mixed with little water together with lemon juice or eucalyptus oil. The tobacco powder is blended with the water-ash mixture forming a highly irritant snuff (20).
In manufacturing African chewing tobaccos the ingredients used include besides salts also lime and different resins.
In South America, powdered smokeless tobacco is known as "rapé ". Rapé is prepared with ingredients like lime, frequently with ash as well as different herbs and barks. Additives, such as chili or cocoa powder, are also used. Rapé is most widespread among the indigenous peoples of the Amazon Basin (20).
Besides *Nicotiana tabacum* there are several other *Nicotiana* varieties known today, most of them growing in Asia, Africa and South America (21). These varieties differ in their alkaloid composition and, consequently, toxicity. Some of them, e.g. *Nicotiana rustica*, *Nicotiana glauca* and *Nicotiana nepalensis*, are used for smokeless tobaccos outside Europe and the USA (19). Therefore, the toxicity of these types of smokeless tobaccos and their health effects may be quite different from today's smokeless tobaccos consumed in Europe and the USA.

3. REGULATIONS FOR SMOKELESS TOBACCOS IN EUROPE

In Austria, chewing tobaccos and nasal snuff were regulated in the past by the Austrian Food Law. Therefore, the detailed provisions concerning raw materials, their quality and the relevant test methods were documented in the Codex Alimentarius Austriacus (22). Today, smokeless tobaccos are regulated by the Austrian Tobacco Law of 1995 (23) in compliance with the EU Directive 2001/37/EC (24). In Germany, the production of smokeless tobacco products is subject to the rules of the German Preliminary Tobacco Law (25) in combination with other Ordinances, e.g., the Aroma Ordinance (26), the Ordinance on Additives (27), the Ordinance on Pesticide Residues (28), etc.
In the European Union, smokeless tobaccos are defined and regulated by the EU Directive 2001/37/EC (24). Health warnings must be printed on the packages and the disclosure of additives and ingredients is required. Moreover, the sale of "tobaccos for oral use" is restricted. The definition of tobaccos for oral use is given in Article 4 of the Directive: "For the purpose of this Directive "tobacco for oral use" means all products for oral use, except those intended to be smoked or chewed, made wholly or partly of tobacco, in powered or particulate form, or in any combination of those forms, particularly, those presented in sachet portions or porous sachets, or in a form resembling a food product". With this definition in mind, the sale of dry snuff, moist snuff and Swedish snus is not allowed in the European Union, with the exception of Sweden.
Today, the sale of certain types of smokeless tobacco, such as moist snuff, is also illegal in several countries outside Europe, e.g., in Israel, Saudi Arabia, Japan, Hong Kong, Singapore, Australia and New Zealand (29).
The use of ingredients for manufacturing smokeless tobaccos has a long tradition. One of the first overviews on the ingredients used in the nineteenth and at the beginning of the twentieth century especially by the Austrian-Hungarian Tobacco State Monopoly was published by F. Berka in 1903 and 1904 (30, 31). Various essential oils, such as rose oil, bergamotte oil, citric oil, clove oil and juniper oil, extracts from different roots and barks as well as powders of ground bark were used as aromatic additives in smokeless tobaccos, especially in nasal snuff. The coumarine and dihydrocoumarine containing flowers of yellow sweet clover (*Melilotus officinalis*) and tonka beans were also used in nasal snuff production. *Gallus Aleppo* extracts served as an additive in chewing tobaccos. Other additives were, e.g., paraffin oil, rum, honey, diluted acetic acid, raisins, salt and sugar syrup. Some of these ingredients are still used in smokeless tobacco product manufacturing, the use of others – such as the coumarine containing materials – is forbidden by law in certain countries, for example in Germany (25).
Today, the ingredients used for manufacturing smokeless tobaccos are regulated in several European countries by national laws and ordinances, for instance in Germany (25), the United Kingdom (32) and France (33).
The ingredients of the special type of smokeless tobacco, Swedish snus, are subject to the regulations of the Swedish Food Law (34). In addition, maximum levels for a number of undesired components in the finished product were defined by the leading manufacturer, Swedish Match, in the Gothia Tek Standard (12). Limits are set for nitrite, total TSNAs, *N*-nitroso dimethylamine, benzo[*a*]pyrene and five heavy metals (Table 1). In addition, pesticide residues have to be in compliance with the Company's pesticide policy

Table 1. Maximum allowable levels of trace-level substances in Swedish snus with a standardized water content of 50% (Gothia Tek Standard)

Substance	Maximum level
Nitrite, ppm	3.5
Total TSNAs, ppm	5
N-Nitroso dimethylamine, ppb	5
Benzo[*a*]pyrene, ppb	10
Cadmium, ppm	0.5
Lead, ppm	1.0
Arsenic, ppm	0.25
Arsenic, ppm	2.25
Chromium, ppm	1.5
Pesticides	according to the Swedish Match pesticide policy

(i.e. their internal limits). These components were selected because they had been pointed out by scientists as potential health risks if they occur in too high concentrations. When setting the maximum allowable levels for the individual components Swedish food regulations were considered for guidance (34). It is important to note that the limits apply to products with a standardized water content of 50% (and not to dry weight) to take account of the known variations in finished product water content. In addition, the Standard specifies requirements regarding the declaration of contents (the ingredients used in manufacturing), the declaration of certain components in the product (water, nicotine and salt) and the manufacturing process (regulatory compliance, raw materials used, process integrity and sanitation).

The Gothia Tek Standard stipulates that the limits of the components of concern must not be exceeded. The Company releases information on the average content of the components on a yearly basis (latest for products manufactured in 2008 showing that component levels in all cases remained below the limits, generally by a wide margin). It can be assumed that products manufactured since the mid 1990s were in accordance with the Standard.

4. TOXICOLOGICAL AND EPIDEMIOLOGICAL ASSESSMENT

4.1 *Chemical composition and toxicological considerations*

For analytical chemists, pharmacologists and toxicologists, the characterization of smokeless tobacco products is a challenge of considerable scientific and practical significance. Compared to tobacco products for smoking, however, the task is much less complex as there is no need to consider any chemical constituents or biological effects related to tobacco burning. Consequently, the focus is on the tobaccos used for manufacturing and the smokeless products made from them.

Like for cigarettes, cigars and fine-cut and pipe tobaccos, the raw materials used for smokeless tobacco products manufacturing are derived from several *Nicotiana tabacum* varieties treated by different curing techniques with or without fermentation. In principle, there is no difference in composition between the tobaccos used in Europe and the U.S. for smoking and those for sniffing, sucking or chewing. The specific properties of these tobaccos and – if appropriate – of the additives used in the manufacturing process determine the qualitative and quantitative composition and the toxicity of the finished smokeless tobacco products.

Today, around 4,990 different natural constituents and contaminants are known to occur in tobaccos ready for manufacturing tobacco products (35). Nicotine is the strongest stimulating and pharmacologically active substance in tobacco. Depending on cultivation and processing conditions, a number of toxic and/or genotoxic substances may be present in the tobaccos: constituents, such as *N*-nitrosamines, heavy metals or traces of radioactive elements, and contaminants like pesticide and herbicide residues or certain air-borne impurities.

The physiological effects of nicotine are assumed to be the reason why a large number of people consume tobacco products. The route of nicotine up-take, its pharmacokinetics and bioavailability are responsible for the stimulating effects observed in humans. The faster the release of nicotine from the tobacco product, the rate of absorption and attainment of peak levels, the higher is the likelihood of continued use or abuse by humans (36). When smoking cigarettes, nicotine is rapidly taken up primarily by the lungs. It takes only ten to fifteen seconds after inhaling for nicotine to reach the brain, associated with a marked arterial-venous gradient in the blood (37, 38, 39). Within five minutes peak levels of more than 10 ng/ml plasma can be reached in venous blood (38, 40).

The nicotine content of smokeless tobaccos depends on the type (nasal snuff, oral snuff, products for chewing, etc.) and covers a certain range (less than 1% up to more than 2%). In contrast to cigarette smoking, nicotine is absorbed from smokeless tobaccos primarily via the buccal mucosa or the nasal cavity. One condition for rapid and effective absorption is the presence of un-protonated nicotine in smokeless tobaccos. This depends on the type of tobacco used for manufacturing and the addition of ingredients alkalizing the tobacco. The bioavailability of nicotine from cigarette smoke, oral snuff and various pharmaceutical nicotine delivery products, and information concerning the pharmacokinetics in humans of this alkaloid following uptake by cigarette smoking or the use of smokeless tobacco is discussed in various publications (38, 39, 40, 41). The blood levels of nicotine obtained by consuming smokeless tobacco are comparable to those seen in smokers; a nicotine boost of 10 ng/ml blood plasma was observed within the first 10 minutes of use of oral snuff (42, 43).

4.1.1 *Tobacco specific* N-*nitrosamines* (TSNAs): The presence of *N*-nitrosamines, especially tobacco specific *N*-nitrosamines (TSNAs), in smokeless tobaccos and the importance of these compounds for the health of consumers are a matter of thorough investigation and intense discussion. It is general accepted that the TSNAs *N*-nitrosonornicotine (NNN), 4-methyl-*N*-nitrosamino-1-(3-pyridyl)-1-butanone (NNK), *N*-nitrosoanatabine (NAT) and *N*-nitrosoanabasine (NAB) are not present in green, fresh tobacco. There is only one publication claiming the presence of traces of NNN in green tobacco (44). However, the

observation was never confirmed. Much rather, TSNAs are generated from nicotine and the minor tobacco alkaloids (nornicotine, anabasine, anatabine) during the curing and fermentation processes in the presence of nitrite or nitrogen oxides (45, 46).

Nitrite itself is not a natural tobacco constituent. It may be formed from nitrate by anaerobic microorganisms during air curing (47, 48, 49). The nitrogen oxides, which contribute to the generation of TSNAs especially in Virginia tobaccos (50), may arise from direct heating techniques during flue curing and from fire curing. These facts are important to understand as they provide an intervention option for reducing or preventing the occurrence of TSNAs in processed tobaccos.

The tobacco specific nitrosamines (TSNAs) were evaluated by the International Agency on Research on Cancer (IARC) in 1985 (51). While there were no appropriate data available for humans, sufficient evidence for carcinogenicity was seen in animals for NNN and NNK and limited evidence for NAB. The data in animals were inadequate for NAT.

In an overall evaluation approach, the classification in groups was applied to the TSNAs in 1987 (52). NNN and NNK were included in Group 2B (possibly carcinogenic to humans) and NAB and NAT in Group 3 (not classifiable). The re-evaluation by IARC in 2007 (53) classified NNN and NNK as Group 1 (carcinogenic to humans) and left NAB and NAT in Group 3.

The presence of TSNAs in smokeless tobacco products was first shown in 1979 by HOFFMANN and coworkers at the American Health Foundation (54). In the 1980s, the problem was intensively pursued by this group (55, 56, 57, 58, 59, 60, 61) and others (62) – focused on moist snuff and only occasionally including chewing tobacco and dry snuff. It should be noted that all analytical data collected were for smokeless tobacco products from the U.S. market. In 1986, TSNA levels up to 80 ppm were found in one of the leading brands of U.S. moist snuff (56).

The research on TSNAs and smokeless tobacco done by the group of HOFFMANN and their historical data continue to form the basis for the IARC classification of NNN and NNK and smokeless tobaccos as carcinogenic to humans (53).

In 1993, DJORDJEVIC *et al.* (63) took an interesting look at the development of TSNA levels between 1980 and 1992 in the two leading U.S. snuff brands (the combined market share in 1992 was 84%). NNN levels on dry weight basis were down to 6.4 ppm and 5.7 ppm (a reduction of 76% and 85%, resp.), NNK levels to 0.5 ppm and 0.7 ppm (minus 89% and 71%) and NAT/NAB levels to 3.6 ppm and 3.9 ppm (minus 84% and 91%). Obviously, products had changed considerably during the time period under investigation.

However, this trend was interrupted by one new snuff brand on the U.S. market, which temporarily (1990 and 1991) showed exceptionally high TSNA levels exceeding competitors' products five- to ten-fold (63). This observation clearly points to two requirements: It calls for the establishment of a product quality standard, as is the case in Sweden for snus (a special type of moist snuff) since the early 1990s (12), and it emphasizes the need for great care in the interpretation epidemiological studies with smokeless tobaccos where the characteristics of the investigated products are not fully understood and documented.

A rather broadly based study by BRUNNEMANN *et al.* in 2000 (64) investigated two major U.S. brands of oral moist snuff (multiple samples purchased in five different states) and shed additional light on the development as well as diversity of this type of smokeless tobacco. One brand, in 2000 and on dry weight basis, had a total TSNA level of 4.6 ppm while the other had 37.6 ppm. The authors had data at hand for a revealing comparison with results from earlier studies of the same two brands. In 1986, total TSNA levels were 18.4 ppm and 80 ppm, resp. (56) and in 1994, 4.1 ppm and 17.2 ppm, resp. (65). Evidently, the manufacturer of one brand was able to bring total TSNA levels down over time and keep them consistent, while for the other brand, levels stayed high and variable. In conclusion, not all brands of similar type are the same!

A review of the historical and current TSNA levels in different smokeless tobacco products was put together in 2004 by RODU and JANSSON (7). Interestingly, this was part of an evaluation of the risks and determinants of smokeless tobacco related oral cancer, Regarding products of the U.S. market, a compilation of published data showed that in moist snuff total TSNA levels (on dry weight basis) were rather variable up to 1991 – occasionally with particularly high values up to around 300 ppm. From 1992 to 2002, levels did not exceed 20 ppm (with one exception). Dry snuff products, evaluated in 1987 and 1989 had total TSNAs of 25–143 ppm. On the other side, chewing tobacco samples analyzed in 1985 and 1989 were as low as 3.5 ppm and 2.3 ppm, resp.

Recognizing the scarcity of data for current (2003) products (only one study since 1995), RODU and JANSSON (7) analyzed TSNAs in several brands (identified in their paper) of U.S. moist snuff, dry snuff and chewing tobacco – along with cigarettes and three smokeless products of a different type for comparison. A new method for TSNA determination involving liquid chromatography-tandem mass spectrometry was used (66). Moist snuff (7 brands) had total TSNA levels (on dry weight basis) of 4.5–12.3 ppm, dry snuff (4 brands) of 6.0–65 ppm and chewing tobacco (four brands) of 1.5–4.7 ppm.

The course of smokeless tobacco product development in the U.S. was followed by STEPANOV *et al.* (8, 67). When they analyzed products purchased between August 2006 and August 2007 the trend for TSNA reduction in recently launched products was confirmed. Total TSNA levels (on dry weight basis) in nine new spit-free moist snuff product styles were between 1.33 ppm and 3.72 ppm; for the three styles of a modified moist snuff brand (no longer on the market) total TSNAs ranged from 3.01 ppm to 6.19 ppm. These values are clearly lower than those for traditional moist snuff brands at 6.27–12.0 ppm.

Turning away from the U.S. to a different geographical region, Scandinavia, where a special kind of oral moist snuff – Swedish snus – has gained significant acceptance since the 1980s, the problem of TSNA levels in smokeless products appears in a different light for two reasons: Swedish snus is manufactured by a process that is less prone to TSNA formation, and the challenge of controlling TSNA levels was met by the establishment of a (voluntary)

Table 2 Contemporary types of smokeless tobacco products on the Canadian market (69)

Product type	Use	Country of origin	Number of styles examined in (69)
Moist snuff, fine-cut	oral	United States	2
Moist snuff, long-cut	oral	United States	13
Moist snuff, pouched	oral	United States	4
Moist snuff, pouched, snus style	oral	Sweden	2
Low-moisture snuff	nasal	United Kingdom	6
Chewing tobacco, loose-leaf or plug	oral	United States	2
Chewing tobacco, Indian-style	oral	India	1

standard – the Gothia Tek Standard (12) – regulating TSNAs and several other undesirable constituents.

In their 1993 study of U.S. moist snuff brands, DJORDJEVIC *et al.* (63) included also three Swedish snus products and compared data for individual TSNAs measured in 1980 to those in 1990. On average, NNN levels (on dry weight basis) went down from 8.24 ppm to 5.39 ppm, NNK from 1.77 ppm to 1.63 ppm and NAT/NAB from 5.02 ppm to 2.98 ppm.

An in-depth investigation of Swedish snus was published in 2004 by ÖSTERDAHL *et al.* (68). It demonstrated a remarkable drop in TSNAs between 1983 and 2002 from an average of 16.2 ppm for total TSNAs to 2.2 ppm (16 and 23 brands, resp., analyzed and data recalculated for dry weight assuming a moisture content of 55%). Regarding current products, in thirteen brands of the leading manufacturer on the Swedish market in 2001, total TSNAs were measured to be between 1.8 ppm and 3.6 ppm (recalculated). For 2002, the leading manufacturer's brands (seven analyzed) had total TSNA levels of 1.8–2.4 ppm (recalculated) and fifteen brands of smaller manufacturers showed levels between 0.3 ppm and 6.7 ppm (recalculated). It is interesting to note that the data indicate manufacturer-specific differences – some values above and others below those of the leading manufacturer.

These data were confirmed by RODU and JANSSON (7) when they considered Swedish snus in their assessment of 2003 products. For five different brands, total TSNA levels (on dry weight basis) were as low as 2.0–2.2 ppm.

Two recent publications took a look at specific markets. MCNEILL et al. (18) sampled smokeless tobacco products available in the United Kingdom. Due to EU regulations these did not include oral snuff (dry or moist). Much rather, the study was focused on products similar to those commonly used in Southern Asia. The approach was open-minded enough to include dried tobacco leaf and tobacco-containing tooth cleaning powder and produced numbers across a wide range for total TSNAs (not detectable – 29.7 ppm) and other analytes. TSNA data for the two reference samples of moist snuff (obtained from Sweden and the U.S.) were as expected. The variation of 130-fold for total TSNAs across all smokeless samples tested, as stated by the authors, is formally correct but gives a totally misleading impression when quoted for "smokeless tobacco products" without any explanation (as done in the abstract and, consequently, in the secondary literature).

RICKERT *et al.* (69) performed a comprehensive chemical and toxicological study of commercial smokeless tobacco products available on the Canadian market in 2008 (imported from the U.S., the U.K., Sweden or India). The approach taken by the authors is distinguished by several features: the full awareness of the need to understand precisely which kind of smokeless tobacco product is under investigation (in the study, products are divided up in seven distinct types; see Table 2); the use of contemporary samples, this way reflecting the present state of product development; the considerate use of analytical methodology; the avoidance of any inappropriate commingling of results for different products; and the reference to the one established (voluntary) standard for smokeless tobacco products (specifically, for Swedish snus), the so-called Gothia Tek Standard (12).

All brand-styles in the study were characterized by measuring ammonia, 1,2-propylene glycol, glycerol, dry matter, nicotine, nitrate and pH. Moist snuff products manufactured in the U.S. (fine-cut, long-cut or pouched) had a total TSNA content (on dry weight basis) of 8.8–14.6 ppm. On the other hand, total TSNAs were much lower in Swedish snus at 2.1–2.5 ppm.

Data for TSNAs in smokeless tobacco products other than oral snuff (dry, moist and snus) are relatively scarce. Samples of chewing tobaccos were occasionally included in studies and showed in most cases comparatively low levels of individual and total TSNAs. As mentioned above, RODU and JANSSON (7) measured total TSNAs (on dry weight basis) of 1.5–4.7 ppm in four brands of chewing tobacco, which were on the U.S. market in 2003. ÖSTERDAHL *et al.* (68) published TSNA data produced over a period of ten years (1983–1992) with samples of chewing tobaccos from Sweden, Denmark and the U.S. Total TSNA levels were between 0.3 ppm and 7.5 ppm (data recalculated for dry weight assuming a moisture content of 15%) with no obvious trend over time. In the study of RICKERT *et al.* (69), two brands of U.S.-style chewing tobacco showed total TSNA levels of 1.6 ppm and 3.4 ppm, respectively.

Data are available for the TSNA content of German nasal snuff. Three brands manufactured in Bavaria were studied in 2004 (70) and had all total TSNA levels below 3.8 ppm on dry weight basis (see Table 3).

The six styles of U.K.-made low moisture nasal snuff ("Scotch") examined by RICKERT *et al.* (69) were found to contain total TSNAs at levels between 1.9 ppm and 3.2 ppm.

4.1.2 *Other constituents and contaminants*: While the tobacco specific *N*-nitrosamines are clearly in the spotlight regarding the analytical characterization of smokeless tobacco products, other constituents and contaminants deserve attention as well because of their toxicological or

Table 3. TSNA levels on dry weight basis in German nasal snuff products (70)

Brand	Water content (%)	NNN [a] (ppm)	NNK [a] (ppm)	NAT [a] (ppm)	NAB [a] (ppm)	Total (ppm)
Brand A	24	1.9	0.7	0.9	< 0.2	< 3.7
Brand B	23	1.8	0.5	1.0	< 0.2	< 3.5
Brand C	17	2.0	0.7	0.9	< 0.2	< 3.8

[a] Abbreviations: NNN = *N*-Nitrosonornicotine, NNK = 4-Methyl-*N*-nitrosamino-1-(3-pyridyl)-1-butanone, NAT = *N*-Nitrosoanatabine, NAB = *N*-Nitrosoanabasine.

Table 4. Content (calculated for dry weight) of trace-level substances, regulated by the Gothia Tek Standard, in contemporary smokeless tobacco types [a]

Trace-level substance	Gothia Tek Standard (12)	Swedish moist snuff (snus) 2008 (12)	Swedish moist snuff (snus) 2008 (69)	U.S.moist snuff fine-cut 2008 (69)	U.S. moist snuff long-cut 2008 (69)
Nitrite, ppm	7	<1.0–3.4	n.a.	n.a.	n.a.
Total TSNAs, ppm	10	1.0–2.0	2.1–2.5	10.5–13.7	8.8–14.6
NDMA, ppb	10	<1.0–1.6	n.a.	n.a.	n.a.
B(*a*)P, ppb	20	<1.0–3.0	1.6–2.1	71–82	33–80
Cd, ppm	1	0.4–0.8	0.97–0.99	0.94–1.03	0.81–1.00
Pb, ppm	2	0.16–0.4	0.2	0.4	0.3–0.4
As, ppm	0.5	<0.06–0.22	0.1–0.2	0.3–0.4	0.2–0.4
Ni, ppm	4.5	<1.0–3.0	1.4–1.5	1.3–1.4	1.2–1.4
Cr, ppm	3	0.4–1.8	1.6–2.0	1.2–1.3	0.8–1.1

Trace-level substance	U.S. moist snuff pouched 2008 (69)	U.S. chewing tobacco 2008 (69	German nasal snuff 2007 (72)	U.K.nasal snuff 2008 (69)
Nitrite, ppm	n.a.	n.a.	<1.0	n.a.
Total TSNAs, ppm	9.0–14.2	1.6–3.4	3.7	1.9–3.2
NDMA, ppb	n.a.	n.a.	n.a.	n.a.
B(*a*)P, ppb	21–81	<LoQ	3.0	12–19
Cd, ppm	0.92–1.09	0.48–0.53	0.93	0.30–0.37
Pb, ppm	0.4	0.3–0.4	0.87	0.6–1.2
As, ppm	0.3	0.2	0.30	0.4
Ni, ppm	1.2–1.6	0.8–1.7	0.76	1.5–2.0
Cr, ppm	1.0–1.4	0.7–1.2	4.5	1.3–2.2

[a] Abbreviations: NDMA = *N*-Nitroso dimethylamine; n.a. = not analyzed, <LoQ = below the limit of quantitation.

carcinogenic potential. There are few studies, which produced data on analytes such as carbonyls, volatile *N*-nitrosamines like *N*-nitroso dimethylamine, polycylic aromatic hydrocarbons (PAHs), especially benzo[*a*]pyrene (B(*a*)P), heavy metals and polonium-210 (^{210}Po). Early reviews of the carcinogens detected in smokeless tobaccos were prepared by HOFFMANN *et al.* in 1987 (57) and by BRUNNEMANN and HOFFMANN in 1992 (71).

The observation made in 2006/2007 by STEPANOV *et al.* (8) that recently launched U.S. moist snuff brand styles were lower in TSNAs than traditional brands is also true for several other constituents. It was clearly the case for nitrite, nitrate, chloride and sulfate; phosphate and formate differed to a lesser degree. The average levels were much lower in new products for the aldehydes, formaldehyde, acetaldehyde and acrolein, with crotonaldehyde being the exception. Very striking reductions were also seen in a range of seven PAHs, including benzo[*a*]pyrene, where levels in new product styles were down to a few percent of those found in the traditional smokeless products. This is a telling example for (desirable) product modification in recent years.

In 2008, trace-level contaminats were determined by RICKERT *et al.* (69) in a broad range of contemporary smokeless tobacco products on the Canadian market. Analytes include the heavy metals, cadmium, chromium, nickel, lead, arsenic and selenium, as well as benzo[*a*]pyrene. RICKERT's data are summarized in Table 4 together with comparable information on Swedish snus and German nasal snuff and the maximum allowable levels of trace-level substances in Swedish snus set by the Gothia Tek Standard (12).

4.1.3 *Summary of analytical data for contemporary products*: A review of the long-known analytical data for smokeless tobacco products is useful for two purposes: to demonstrate the changes (generally the progress from a risk point of view) in product characteristics over the years; and to alert scientists to the fact that contemporary products are quite different from the ones, for which epidemiological evidence was gathered in studies conducted decades in the past.

It is interesting to see how contemporary smokeless tobacco types in the U.S. and in Europe compare with the Gothia Tek Standard (12) (originally developed for Swedish snus), which is more and more considered by health experts, regulators and manufacturers as a possible approach to managing trace-levels constituents and contaminants. The data in Table 4 are compiled using results of recent analytical studies.

It is quite obvious that three types of products are in compliance with the Gothia Tek Standard: (a) the various brand-styles of Swedish moist snuff (snus) based on summary data released by the leading manufacturer in Sweden for products made in 2008 (12) and the results of RICKERT *et al.* (69); (b) the two brand-styles of U.S.-type chewing tobacco analyzed by RICKERT *et al.* (69); and (c) the brand-styles of low-moisture nasal snuff of U.K. origin examined by RICKERT *et al.* (69) and of German origin as shown by data of the leading manufacturer in Germany (72), chromium being the one trace-level constituents above the Standard (coming either from the soil or from cutting and grinding equipment or from packaging material).
On the contrary, all U.S.-type moist snuff (fine-cut, long-cut and pouched) brand-styles failed to meet the Gothia Tek Standard. While heavy metals generally remain below the limits, total TSNAs were higher than the Standard's 10 ppm in most products and benzo[a]pyrene was above the 20 ppb limit in all U.S. moist snuff styles – often quite considerably. Again, these data emphasize the need for unequivocal differentiation of smokeless tobacco products by scientists and consumers particularly if they look rather similar such as the different types of moist snuff.

4.1.4 *In vitro toxicological assessment*: The assessment of the toxicological potential by in vitro methods is well established for tobacco products that are consumed by smoking. The focus here is on the smoke. As no smoke is produced when smokeless tobacco products are consumed the substrate of interest for toxicological studies is the product itself.
In 1987, CURVALL *et al.* investigated the mutagenic activity of concentrates of 24-h urine provided by users of snus (Swedish moist snuff), cigarette smokers and non-tobacco users (73). Mutagenicity was assayed using the strain TA98 of *Salmonella typhimurium*, both in the presence and absence of S9 mix. The mutagenic activity of smokers' urine on average was significantly higher than with snuff users, abstinent snuff users and non-tobacco users. No significant difference in mutagenic activity was found between the urine of snuff consumers, whether currently using or abstaining from snuff, and the urine from non-tobacco users. It is of interest that there was no significant difference in urinary nicotine and cotinine levels between snuff users and smokers.
The genotoxicity of aqueous and methylene chloride extracts of Swedish moist snuff was examined in 1991 by JANSSON *et al.* (74). The test systems were selected to provide the best data for estimating carcinogenicity (Ames tests with the strains TA98, TA100, TA1535 and TA1537 of *Salmonella typhimurium*; sister chromatid exchange in human lymphocytes; chromosome aberrations and gene mutations in V79 Chinese hamster cells; micronuclei in mouse bone marrow cells; induction of sex-linked recessive lethal mutations in *Drosophila melanogaster*). Based on the results the authors characterized the carcinogenic potential of Swedish moist snuff as low. .
RICKERT *et al.* (69) made an attempt to measure and compare the cytotoxic, clastogenic and mutagenic properties of extracts of contemporary smokeless tobacco products using the Health Canada Official Methods widely utilized in cigarette research (75, 76, 77). The method to measure mutagenicity was adapted for testing tobacco extracts by RICKERT *et al.* (78). So far, this work was not all too successful due to the weak inherent activity of the materials and the possible interference by as yet unidentified factors.

4.2 *Epidemiological assessment*

The number of epidemiological studies with smokeless tobacco products performed since the early 1950s is very large. The driving force was the investigation of the health effects observed in smokeless tobacco users and, more prominently in the course of time, the comparison of tobacco smoking and smokeless tobacco consumption. Every methodological approach possible has been taken for examining smokeless tobacco products. As in other fields, great care has to be taken in analyzing and evaluating the wealth of published material in a critical and responsible way. In the case of smokeless tobacco, one element is particularly important:
A pivotal aspect of the quality and informative value of an epidemiological study is the knowledge and clear description of which kind of smokeless product was investigated. This indispensible requirement is not met sufficiently in many studies. In view of the diversity of smokeless products even in a distinct geographical area, such as the United States or Scandinavia, and the changes effected by commercial product development over time, studies with unclear product characterization are scientifically useless and only blurring the vision.
A similar serious problem along this line is the approach taken in certain reviews when combining data for products, which are clearly different in origin, composition and/or date of manufacture. In some cases, this is done without hesitation as a basis for sophisticated statistical evaluation, and in others in a way so unrestrained that it is not difficult to guess the purpose. However, there are several gratifying examples of reviews applying stringent criteria of scientific scrutiny and honesty.
The epidemiological evidence of the health effects of smokeless tobacco consumption has been collected and evaluated in a number of useful reviews published since the 1980s. Taken together, they cover and sort the multitude of studies available until 2009. Some of them are focused on one or several specific health endpoints while others take a broader look at the health implications of smokeless tobacco use. These reviews differ widely regarding critical approach, comprehensiveness and intention. In this paper the reviews are divided into two groups, reviews across several health outcomes (see 4.2.1 below) and reviews on specific health outcomes in combination with selected pertinent studies (see 4.2.2 below).

4.2.1 *Reviews across several health outcomes*:
a) IARC 1985 and 1987: One of the first overall evaluations on smokeless tobacco and cancer was conducted by the International Agency on Research on Cancer (IARC) in 1985 (51). The detailed evaluation clearly distinguished the various types of smokeless tobacco. It was concluded that there was sufficient evidence that the oral use of snuff of the types commonly used in North America and Western Europe was carcinogenic to humans, and that there was limited evidence that chewing tobaccos of the types commonly used in these

areas were carcinogenic. It was also concluded that there was inadequate evidence that the nasal use of snuff was carcinoenic to humans.
Two years later and with little additional evidence IARC (52) classified smokeless tobacco altogether as Group 1 (sufficient evidence for carcinogenicity for humans). This evaluation was based primarily on historical epidemiological data from the U.S. and the investigations of HOFFMANN´s group. It should be kept in mind that the quality and levels of toxic components of the smokeless tobacco types consumed before the mid 1980s were quite different from those of the products on the U.S. and European markets today.

b) CRITCHLEY and UNAL 2003: A review on the association between smokeless tobacco use and different health effects, such as cardiovascular diseases, oral cancer in general, esophagus and gastric cancer was published in 2003 by CRITCHLEY and UNAL (79). A well considered search strategy was used for the identification of primary studies by using an electronic data base followed by the rating of the papers identified by two independent reviewers. Assessment was performed with due consideration to smokeless tobacco type and geographical area. Endpoints were clearly defined. CRITCHLEY and UNAL concluded that most recent studies from the U.S. and Scandinavia showed no significantly elevated risks while moderate positive associations could not be ruled out due to lack of statistical power. Especially regarding cardiovascular disease further rigorous studies were called for.

c) ROTH *et al.* 2005: In 2005, ROTH *et al.* (80) compared the use of Swedish snus and smoking concerning health risks on the basis of published data. They reviewed the literature for studies that provided quantitative risk estimates associated with Swedish snus and cigarettes in the very same population and were done under strict control of confounders. Seven studies were identified that addressed eight health outcomes. Especially for lung cancer, oral cancer, gastric cancer, cardiovascular disease and all-cause mortality, the health risks associated with snus use were found to be substantially lower than risks from smoking

d) BROADSTOCK 2007: An impressive systematic review of the health effects of smokeless tobacco products was published in 2007 by M. BROADSTOCK in a New Zealand Health and Technology Assessment (NZHTA) Report (81). The review was funded under contract by the New Zealand Ministry of Health. NZHTA was commissioned to undertake this review to support the Ministry's policy considerations regarding harm minimization in tobacco consumers. The association between smokeless tobacco and the risk for different cancers, cardiovascular disease, stroke, diabetes, pregnancy outcome and certain inflammatory diseases was evaluated. Studies included in the review had to be in accordance with strict selection criteria. The focus was on smokeless tobacco products, which had been modified to reduce toxicants compared to conventional tobacco products or which were offered to consumers as being less harmful alternatives to conventional tobacco products. Studies comparing the risks for users of modified smokeless tobacco products with non-tobacco users and users of conventional combustible tobacco products, such as cigarettes, were included in the review. The sample size of a study considered worthy of evaluation had to be at least 100 participants. The careful control of critical confounders, including age, sex, alcohol consumption and the use of other tobacco products was an essential inclusion criterion. Studies were excluded if they did not provide data for the type of modified smokeless tobacco under consideration.
Out of 217 publications only 16 studies and two systematic reviews met these rigid inclusion criteria. BROADSTOCK came to the conclusion that the relevant published epidemiological studies showed smokeless tobacco consumption, especially the use of Swedish moist snuff, carrying – if any – a much lower risk for cancer of the head, neck and gastrointestinal tract than smoking. For non-fatal and/or fatal cardiovascular disease in men, most studies found no difference in Swedish moist snuff consumers compared to subjects with no tobacco use. Nevertheless, a slightly increased risk of dying from cerebrovascular and cardiovascular diseases could not be excluded. BROADSTOCK recognized the possibility of adverse effects in pregnancy from the use of Swedish snuff. No significant risk of diabetes for snus users was observed.

e) IARC 2007: The association between smokeless tobacco use and cancer was re-evaluated in an IARC Monograph published in 2007 (53), which considered the relevant literature up to 2003/04. Again, smokeless tobacco was classified as "carcinogenic to humans" (Group 1). For the assessment, data of toxicological, epidemiological and behavioral studies from all over the world were used.
As pointed out earlier the smokeless tobacco products consumed today in Europe and North America differ substantially from the smokeless tobacco materials used in Asia, Africa and South America regarding manufacturing process, chemical composition, toxicity and potential carcinogenicity. Even in today's Western markets product characteristics may be quite different depending on the type of product
Criticizing the overall conclusion by IARC that "smokeless tobacco" was "carcinogenic to humans" NITZKIN and RODU (82) emphasized that the distinction between the higher risk profile of U.S. dry snuff and the minimal risk conferred by chewing tobacco and moist snuff were ignored in the section "health effects" of the 2007 IARC report although this distinction was in fact made in the section "smokeless tobacco use". It is difficult to understand why IARC failed to discriminate between the cancer risks of the different smokeless tobacco products.

f) BOFFETTA *et al.* 2008: In 2008, BOFFETTA *et al.* (83) published a review on the consumption of smokeless tobacco and cancer risk. They concluded that epidemiological data from the U.S. and Asia showed an increased risk for oral cancer (overall RR = 2.6; 95% CI: 1.3–5.7), which was not confirmed in studies from Scandinavian countries (RR = 1.0; 95% CI: 0.7–1.3). A slightly increased risk for esophageal and pancreatic cancer was found in studies from northern Europe. The results for lung cancer were inconsistent, with northern European studies suggesting no increased risk. Cancer risk of smokeless

tobacco users was found to be "probably" lower than that of smokers, but higher than that of non-tobacco users. The approach and conclusions of BOFFETTA *et al.* were criticized by LEE and HAMLING (84) on grounds of inconsistent use and arbitrary selection of risk ratios used in the meta-analysis (disussed below in detail).

g) LEE and HAMLING 2009: LEE and HAMLING (85) evaluated in 2009 the relation between smokeless tobacco and cancer in a systematic review of published epidemiological studies. The review was restricted to studies in Western populations; in practice this meant studies in the U.S. and Scandinavia. Consequently, the two major types of smokeless tobaccos commonly used in these countries were considered, namely chewing tobacco and snuff (snus in Sweden). Eighty-nine studies were identified as suitable for meta-analysis, among them 62 from the U.S. and 18 from Scandinavia. Only 46 (52%) of the 89 studies had controlled for smoking. Meta-analyses were conducted overall and for the U.S. and Scandinavia separately taking account of all available estimates. This broad spectrum was used to avoid any data selection bias.
Potential associations between smokeless tobacco use and oropharyngeal, esophageal, stomach, pancreas, other digestive, larynx and nasal, lung, prostate, bladder, kidney, hematopoietic and lymphoid cancers was examined. Analyses based on smoking adjusted estimates for most cancers under investigation showed no indication of increased risk of cancer for snuff, as used in Sweden. The crude data for oropharyngeal cancer revealed a significantly increased risk associated with smokeless tobacco use, but this was not evident for estimates adjusted for smoking and alcohol or for studies published since 1990. Any effects of smokeless tobacco were related mainly to products used in the U.S. in the past. A weak but ~~a~~ significant association with prostate cancer, based on limited data from U.S. studies, was judged to require more confirmatory evidence. According to LEE and HAMLING the cancer risks from smokeless tobacco products as used in North America and Europe were clearly much lower than those from smoking and not evident at all in Scandinavia.
LEE and HAMLING (85) were not able to confirm the conclusions of BOFFETTA *et al.* (83), especially the significant association of smokeless tobacco with pancreatic and esophageal cancer. The reasons for these remarkable differences were commented on in a separate paper by LEE and HAMLING (84). The authors pointed out that their review (85) offered a more robust meta-analysis of the data than conducted by BOFFETTA *et al.* (83) for a number of reasons. One was the use of published as well as derived estimates, which added considerably to the data available for analysis. Other reasons were the assurance that all relative risks used were in fact adjusted for smoking and the use of a predefined systematic procedure to decide which estimates to include in the meta-analysis.
Another discrepancy between the two reviews was the way BOFFETTA *et al.* (83) selected the RRs used in their meta-analysis from the published literature. "Boffetta *et al.* included some clearly biased or not smoking-adjusted estimates" (84). This had a large effect on the outcome for pancreatic cancer and esophageal cancer. For example, in the case of pancreatic cancer significant risk increases for never smokers in one study (86) and for smokers and non-smokers combined in another study (87) were selected by BOFFETTA *et al.* while ignoring estimates showing no risk increase for smokers and non-smokers combined in the first study (86) and for never smokers in the second (87). Regarding esophageal cancer, the study by ZENDEHDEL *et al.* (88) showed a significantly increased relative risk for squamous cell carcinoma among never smokers but no risk increase for adenocarcinoma among never smokers and no risk increase for either cell type among smokers and non-smokers combined. BOFFETTA *et al.* (83) elected to include only the significant RR, despite the inherent bias from such a procedure.
In addition, LEE and HAMLING (84) criticized the statement of BOFFETTA *et al.* (83) that the cancer risk of smokeless tobacco users was "probably" lower than that of smokers. For the four cancers considered by BOFFETTA *et al.* (lung, esophagus, oropharynx, pancreas) the relative risks were found to be substantially lower in smokeless tobacco users than in smokers (e.g., for lung cancer a 20% risk increase for smokeless tobacco users up against a 20-fold increase in current smokers and a 10-fold increase in former smokers). To LEE and HAMLING it was unclear why BOFFETTA *et al.* did not accept that the risk for smokeless tobacco users was clearly much lower than for cigarette smokers. On basis of the risk estimates arrived at by LEE and HAMLING, the attributable deaths from all smoking related cancers would be almost 100 times lower if smokeless tobacco would be consumed for lifetime rather than cigarettes smoked.

4.2.2 *Reviews and studies on specific health outcomes*: The reviews presented above were published between 1987 and 2009. Not all investigated associations between specific diseases and smokeless tobacco consumption are evaluated and discussed in these reviews. More recently, additional dedicated reviews and major studies have looked at smokeless tobacco use in the United States and Sweden. They are too new to be included in any of the earlier reviews. These reviews and studies are now discussed separately.

a) Cancer of the oral cavity, the larynx and the pharynx: Studies concerning the association between smokeless tobacco use and cancer of the head and neck, including oral cavity and pharynx, were conducted by WYNDER *et al.* (89), WINN *et al.* (90), MASHBERG *et al.* (91), BOUQUOT *et al.* (92) in the U.S., and by SCHILDT *et al.* (93), LEWIN *et al.* (94) and ROSENQUIST *et al.* (95) in Scandinavia. An increased risk from the consumption of smokeless tobacco was found in U.S studies conducted before 1990 (89, 90) but not in those from Scandinavia (93, 94, 95).
In 2002, after adjustment for confounders such as smoking, alcohol drinking, etc., no association between smokeless tobacco use and all cancer mortality – including cancer of the oral cavity – was found in the U.S. by ACCORT *et al.* (96).
In 2002, RODU and COLE (97) identified 21 epidemiological studies, primarily case-control studies, which investigated the risk of smokeless tobacco consumers for developing cancers of the oral cavity and upper respiratory tract. They found that the use of chewing tobacco and moist snuff was

associated with relative risks (RRs) of 0.6 to 1.7 for cancer of the oral cavity and the upper respiratory tract. These RR values were generally not significantly different from 1; that means no elevated risk was found. The consumption of U.S. dry snuff was associated in 4 studies with an overall RR of 5.9 (95%: C.I. 1.7–20), while for unspecified types of smokeless tobacco RR values between 1.5 and 2.8 were reported. These findings clearly indicate the need for differentiating the various products types under investigation. Two years later, another review on the association between smokeless tobacco and oral cancer was published by RODU and JANSSON (7) in combination with a detailed discussion of the development of the TSNA levels in smokeless tobacco products. This review is remarkable in that it challenged the established wisdom of the compelling relationship between Western-style smokeless tobacco consumption and oral cancer.

LUO *et al.* (86) could not detect an increase of oral cancer risk in Swedish snus users among the Swedish Construction Workers Cohort compared with never users of any tobacco.

In 2007, WEITKUNAT *et al.* (98) evaluated 32 epidemiological studies published between 1920 and 2005 for the relation between European and American smokeless tobacco and oral cancer. As the first step, they performed a meta-analysis of all available studies. Subsequently, they grouped the studies according to rather basic criteria, such as geographical origin (e.g., USA and Scandinavia) and year of publication. This way, interesting patterns were recognized for the risk ratio (RR) levels. Tests for homogeneity and publication bias were included. The computed significantly increased risk of 1.87 was mainly due to studies published before 1980. No risk increase was seen in studies from Scandinavia. The authors concluded that smokeless tobacco, as used in the U.S. or Europe, carries at most a minor increased risk of oral cancer. However, elevated risks in specific populations or from special products could not definitely be excluded [a].

ROOSAAR *et al.* (100) reported a statistically significant increase in the incidence of the combined categories of oral and pharyngeal cancer among daily users of snus in a cohort from Uppsala, central Sweden, and a slightly increased overall mortality. In the study the effect of snus consumption was documented in 1973/74, without considering any possible changes (regarding snus consumption and other exposures) during the follow-up period of 28 years. The authors recognized that their results were inconsistent with claims that the use of Scandinavian moist snuff (snus) was without demonstrable risk. While relative risks of the outcomes studied were consistently lower than those associated with smoking and the combined previous Scandinavian literature on snus and oral cancer had not shown any association (85, 97, 98) the observed snus related risks were considered biologically plausible. Consequently, ROOSAAR *et al.* asked for further exploration.

Reviews on the association between smokeless tobacco use and cancer of the head and neck, including cancer of the oral cavity, pharynx and larynx were conducted by IARC (51, 53), CRITCHLEY and UNAL (79), ROTH *et al.* (80), BROADSTOCK (81), BOFFETTA *et al.* (83) and LEE and HAMLING (85). These reviews are discussed above.

b) Non-neoplastic oral diseases: Persistent use of smokeless tobacco may cause "snuff pouch keratosis" in the oral cavity, a lesion which was first reported in 1916 (101) among women living in a rural area of Austria and consuming chewing tobacco. Some forms of keratosis may be regarded as pre-cancerosis.

In 1986, BOUQUOT and GORLIN (102) observed a prevalence of less than 1% in the general population. Some lesions were identified as leukoplakias and almost 7% of the leukoplakias examined were either carcinomas or severely dysplastic lesions. Snuff pouch keratosis occurred at the site of smokeless tobacco placement in the mouth of more than 60% of the users (103, 104) within six months to three years of initiation of the habit (105, 106). Its frequency depended on the type of smokeless tobacco used. Moist snuff more often produced this type of keratosis (107). However, according to ANDERSON and AXÉL (108), Swedish moist snuff in pre-portioned pouches caused less pronounced mucosal changes and fewer cases of snuff pouch keratosis than the loose form. Generalization of the findings of ANDERSON and AXÉLL are not appropriate as Swedish moist snuff differs in several aspects (e.g., TSNA content and method of pasteurization) from moist snuff common in other countries.

ROOSAAR *et al.* (109) noted in a cohort study, published in 2006, a strong association between the degree of lesions of the oral mucosa and the current use of Swedish moist snuff. The lesions disappeared in all individuals, who stopped using snus permanently. In no case was an important clinical change for the worse observed regardless whether individuals decreased their use of snus or continued unabatedly. A total of three incident cases of oral cancer were seen in this cohort of 1,115 participants with snus induced lesions during the follow-up period of almost thirty years. None of these cancers occurred at the site of the original lesion. ROOSAAR *et al.* interpreted the results of their study as suggesting that snus induced oral mucosal lesions probably constituted no more than markers of current or recent consumption.

In 2008, KALLISCHNIGG, WEITKUNAT and LEE (110) published a systematic review of the relationship between smokeless tobacco and non-neoplastic oral diseases in Europe and the United States. Epidemiological studies from Europe (mainly performed in Sweden) and from the U.S. published between 1963 and 2007 were considered. Data were assessed separately for oral mucosal lesions, periodontal and gingival diseases, dental caries and tooth loss and oral pain. The strong association of current use of smokeless tobacco, particularly snuff, with the prevalence of oral mucosa lesions was confirmed. The data provided only suggestive evidence for the association of snuff use with gingival recession and reduced tooth firmness as well as the use of chewing tobacco and dental caries. While smokeless tobacco use clearly increased the risk of oral mucosal lesions, conclusions regarding the other endpoints were limited by study weaknesses, including the poor control of confounding factors.

Published studies concerning "snuff pouch keratosis" and smokeless tobacco use were reviewed by IARC (53).

[a] As a footnote, the comments by CONWAY (99) should be noted criticizing the review of WEITKUNAT *et al.* mainly for its origin, presumed purpose and suspected motives and, moreover, for certain methodological details.

c) Cancer of the nasal cavity: Some types of smokeless tobacco are used by nasal inhalation. Therefore, the possibility of cancer of the nasal cavity must be examined.
In 1984, BRINTON and co-workers (111) performed a case-control study investigating the risk for the development of cancer of the nasal cavity and the paranasal sinuses in U.S. nasal snuff consumers. No increased risk was detected. SAPUNDZHIEV and coworkers (112) reported that the chronic abuse of nasal snuff led to morphological and functional changes in the nasal mucosa.
Though nasal snuff contains substances that are potentially carcinogenic there is no firm evidence at present linking the use of nasal snuff to increased incidence of cancer or other malignancies of the head and neck.
According to PFAUE *et al.* (113) cancer of the inner nose and the paranasal sinuses is rarely observed in the general population compared to cancer of the oral cavity. In Germany, it accounts for a total of only 3% of all malignant tumors in the area of the upper aero-digestive tract. Exogenous factors, such as infection by human papilloma viruses or exposure to air-borne carcinogens at the work place, seem to play a more important role in the generation of carcinomas in the nasal area than the use of nasal snuff.

d) Cancer of the esophagus and the gastro-intestinal tract: Up to 2006, only few investigations from Scandinavia were published on smokeless tobacco use and the risk of esophageal or stomach cancer. Most of them suggested an absence of risk (87, 93, 114, 115). In the U.S., an association was found only in older studies as shown by LEE and HAMLING (85).
In a cohort study published in 2008, ZENDEHDEL *et al.* (88) investigated the risk of gastroesophageal cancer in users of Swedish snus. They criticized previous epidemiological studies on snus and esophageal cancer, which showed significantly increased risks, for their limited power and/or insufficient covariate information for eliminating important positive or negative confounders, such as smoking intensity. In their study, ZEHNDEHDEL *et al.* investigated the incidence of stomach and esophageal cancers among 336,381 male Swedish construction workers between 1971 and 2004. The observed cancer cases were divided into esophageal adenocarcinomas, esophageal squamous cell carcinomas and cardia and non-cardia stomach cancers. Although confounding by exposures, which were not captured, and a certain degree of differential misclassification of smoking may have inflated the association (this is discussed in detail in the paper) ZENDEHDEL *et al.* nevertheless concluded that their study provided suggestive evidence for an independent carcinogenic effect of snus. In any case, they reported a significantly increased (by 40%) overall risk for non-cardia stomach cancer among Swedish construction workers using snus compared to non-users.
ZEDEHDEL *et al.* (88) also investigated the association between smoking and gastroesophageal cancer. A dose-response relationship between cigarette smoking and risk for this cancer was reported. An increased risk of gastroesophageal cancer in snuff users was found as well. However, no dose relationship was demonstrated for the association. The participants in this part of the study were only characterized as snuff users or non-users together with their individual smoking habits (non-smokers or smokers of cigarettes, pipes or cigars). Information on daily snuff consumption and the duration or change of the habit during the observation time 1971 to 2004 was not included in the paper. Tobacco exposure information recorded only at the entry of the participants into the cohorts was used in this study. It is well documented that the composition and toxicological characteristics of smokeless tobacco products were altered profoundly in the last decades. Therefore, it has to be assumed that the intensity and quality of exposure of snus consumers to harmful components in smokeless tobacco have changed considerably during the study period.
Reviews of the association between smokeless tobacco use and gastroesophageal cancer were published by IARC (53), BROADSTOCK (81), BOFFETTA *et al.* (83) and LEE and HAMLING (85).

e) Cancer of the pancreas: In a case-control study conducted in five states of the U.S., ALGUACIL and SILVERMAN (116) compared the risk for pancreatic cancer in pipe, cigar and smokeless tobacco users, who had never smoked cigarettes, with that of never tobacco users. The type of smokeless tobacco was not specified. Subjects who used smokeless tobacco regularly had a non-significant RR of 1.4 (95% CI: 0.5–3.6) for pancreatic cancer compared to never users of any tobacco. The conclusion was based on 13 cases only.
The association between Swedish snus and pancreatic cancer was investigated by LUO *et al.* (86) in the Swedish Construction Workers Cohort. An increased risk of pancreatic cancer was detected (RR for ever users of snus: 2.0; 95% CI: 1.2–3.3). This result is in line with that reported by BOFFETTA *et al.* from Norway (87) with an RR of 1.67 (95% CI: 1.12–2.50). The study from Norway was heavily criticized in letters and comments by NILSSON (117), RUTQVIST and LEWIN (118), RAMSTRÖM (119) and RODU and COLE (120). There was no sound adjustment for confounders, such as alcohol and smoking, which may have contributed to the implausible results of the study. Several methodological flaws made the conclusions tenuous and in some respect even misleading and selection biases could not be excluded. The capacity of the tobacco specific *N*-nitrosamine, NNK, to introduce pancreatic tumors in rodents could not be regarded as an additional proof for the association between snus use and pancreatic cancer in men.
In the view of these arguments, RUTQVIST and LEWIN (118) disagreed with the conclusion of BOFFETTA *et al.* (87) establishing a causal relationship between snus and pancreatic cancer.
In a U.S. case-control study HASSAN *et al.* (121) saw no increased risk for pancreatic cancer from the use of snuff or chewing tobacco.
Reviews and meta-analyses on smokeless tobacco use and risk of cancer of the pancreas were prepared by IARC (53), BOFFETTA *et al.* (83), SPONSIELLO-WANG *et al.* (122) and LEE and HAMLING (85).
In a review, SPONSIELLO-WANG *et al.* (122) found that the risk for pancreatic cancer from smokeless tobacco consumption was – if any – in all likelihood small and certainly lower than that from smoking. Epidemiological studies from North America and Scandinavia were included in the analysis. The authors criticized previous findings of an increased risk for pancreas cancer. The relevant studies had various weaknesses, including few exposed cases, reliance

on cohort studies with exposure recorded only at baseline, poor control groups in some case-control studies and lack of dose-response relationship. Publication bias, with certain negative studies not published, was also possible. In addition, consumers of different types of smokeless tobacco products were included in the exposed cohorts.
The meta-analyses of SPONSIELLO-WANG (122) and LEE and HAMLING (85) showed no association between the use of smokeless tobaccos, common in the U.S. and Scandinavia, and pancreas cancer. Again, this is in contrast to BOFFETTA *et al.* (83). The reasons for the divergent conclusions were discussed by LEE and HAMLING (84) along the same lines as with regard to the increased risk for oesophageus cancer determined by BOFFETTA *et al.* (83). As before, differences in the selection of the basic data sets of RRs used for meta-analysis in the reviews were the main determinant.

f) Lung cancer and chronic obstructive pulmonary disease (COPD): Using data from the First National Health and Nutrition Examination Survey (NHANES I) Epidemiologic Follow-up Study, ACCORTT *et al.* examined the 20-year chronic disease mortality experience (96) and the cancer incidence during a period of up to some 20 years (123) in smokeless tobacco users. Unfortunately, the different types of smokeless tobacco consumed and the use habits were not well characterized. No increase in lung cancer mortality was found. Lung cancer incidence relative to non-tobacco users was not increased in males, while an association found in older females has to be viewed with caution on grounds of several obvious confounders, which may have influenced the outcome.
However, in 2005, HENLEY *et al.* (124) found a surprising significant association between smokeless tobacco use and mortality from respiratory system diseases and COPD. This observation was made in the U.S. Cancer Prevention Study No. I (CPS-I) but not confirmed in the U.S. Cancer Prevention Study No. II (CPS-II). In CPS-II, a statistically non-significant increased risk of death from lung cancer was seen, which was not evident in CPS-I. No consistent dose-response relationships were established with both endpoints. According to HENLEY *et al.* these associations may reflect chance, the inclusion of current or former smokers among those, who reported using smokeless tobacco exclusively, or confounding by other unidentified factors.
FOULDS and RAMSTRÖM (125) were skeptical about this finding and stated that "the mechanism whereby use of smokeless tobacco in the mouth may cause cancer of the lung (but not of the oral cavity) and other lung diseases is not clear". The lack of a dose-response relationship with either frequency or duration of smokeless tobacco use cast doubt over the likelihood that the significant relationship found by HENLEY *et al.* represented causal effects. A response to this critique was given by HECHT (126) and HENLEY and THUN (127). HECHT claimed that the presence of TSNAs in smokeless tobacco supported the increased lung cancer risk in smokeless tobacco users (NNK has been shown to be a lung carcinogen in small rodents) but gave no explanation for the reported association between smokeless tobacco and COPD. Henley and Thun also used the TSNA content of smokeless tobaccos as an argument for the lung cancer association, but a plausible reason for the association with COPD was not presented.
In 2007 in their cohort of Swedish construction workers, LUO *et al.* (86) did not observe an increased risk for lung cancer in men who used snus but did not smoke.
The relationship between smokeless tobacco use and lung cancer was reviewed by ROTH *et al.* (80), BOFFETTA *et al.* (83) and LEE and HAMLING (85). An increased lung cancer risk was not reported by any of the reviews.

g) Hypertension, cardiovascular diseases and stroke: The scientific evidence on whether long-term use of moist snuff is associated with hypertension is limited and inconsistent. According to LEE (128) the combined studies from the United States and from Sweden do not demonstrate any chronic effect on blood pressure.
In a prospective study, HERGENS *et al.* (129) investigated the association of long term snuff use and hypertension in 102,930 Swedish construction workers. The use of Swedish moist snuff appeared to be associated with a moderately increased risk of hypertension.
In 2004, GUPTA *et al.* (130) reviewed studies on the association between smokeless tobacco and cardiovascular risk factors and events, which were published between 1966 and 2002. The relation between smokeless tobacco use and hypertension, platelet function, oxidative stress, lipid profile, diabetes, fibrinogen level and cardiovascular mortality together with other health parameters was evaluated. Although the data base for this review was poor and inconsistent regarding endpoints, GUPTA *et al.* concluded that there was an association between smokeless tobacco use and an adverse cardiovascular risk profile. The conclusion is not in agreement with the more recently conducted review by LEE (128).
A similar review was performed by ARABI (131). He concluded that smokeless tobacco consumption modestly increased cardiovascular mortality. It also produced transient changes in heart rate and blood pressure, but did not increase the risk of atherosclerosis or myocardial infarction. The association with diabetes, lipoproteins and stroke was not clear.
In 1994, BOLINDER *et al.* (132) published a paper investigating the association of tobacco use and cardiovascular mortality in the Swedish Construction Workers Cohort. This study population was available owing to the construction industry's implementation of a health examination program. Of the 132,036 participants, 4.7% were smokeless tobacco users, 21.1% smokers, 12.9% ex-smokers, 37.2% "other" tobacco users and 24.1% non-tobacco users. Enrollment was in 1971–1974 with follow-up 1974 through 1985 (for 12 years). While confirming that the risk of dying from cardiovascular diseases was lower for smokeless tobacco users than for smokers, BOLINDER *et al.* observed a significant association between smokeless tobacco use and mortality from ischemic heart disease (RR = 2.0; 95% CI: 1.4–2.9) compared to non-tobacco users in participants aged 35 through 54 at entry into the study, which was not seen in older entrants. No excess mortality was seen from stroke.
The study was criticized by RODU and COLE (133), who stated that the broad spectrum of fatal "effects" and striking age specificity did not seem explicable in biological terms.

A selection bias for the control group had to be assumed. Possible explanations for the slightly increased risk found by BOLINDER *et al.* (132) were discussed by HERGENS *et al.* (134) and LEE (128). There may be differences between the population samples (employed vs. general population). Changes in snuff use and smoking habits while the study period was ongoing, resulting in deviations from the baseline exposure information gathered only once in the early 1970s, are quite likely. The modification of manufacturing techniques and snuff composition during the study period has most probably influenced the outcome of the study (135). These arguments point at the basic weakness of all evaluations of the association between snus use and health risks conducted with data of the Swedish Construction Workers Cohort.

In a study conducted in 2005 in two Swedish counties, HERGENS *et al.* (134) did not find that the use of Swedish moist snuff increased the risk for myocardial infarction in men.

However, in 2007 HERGENS *et al.* (136) reported a relative risk of 0.91 for non-fatal cases of myocardial infarction in snus ever-users of the Swedish Construction Workers Cohort and a significant slightly increased risk of 1.28 for fatal cases. Heavy users (more than 50 grams per day) had a relative risk of 1.96 for fatal myocardial infarction. The authors concluded that ever-use of snuff increased the probability of dying from myocardial infarction.

In a case-control study of 1992 from northern Sweden, HUTHASAARI *et al.* (137) were able to show that in middle-aged men snuff dipping was associated with a lower risk of myocardial infarction than cigarette smoking. The same group reported in 1999 (138) that the risk of myocardial infarction was not increased in snuff dippers compared to never-users of tobacco. In consequence, nicotine itself seemed not to be an important contributor to ischemic heart disease in smokers. A possible small or modest harmful effect of snuff dipping on the risk of sudden death could not be excluded in this study due to the limited number of fatal cases of myocardial infarction. The snuff consumed by the participants in these studies was primarily moist Swedish snuff.

No association between the use of Swedish moist snuff and stroke was observed by ASPLUND *et al.* in a study published in 2003 (139).

JOHANSSON *et al.* (140) reported in 2005 a hazard ratio of 1.62 (95% CI: 0.70–3.03) for coronary heart disease in male Swedish snuff users after adjustment for age; the association was not significant.

HAGLUND *et al.* (141) reported in 2007 no excess risk of mortality or hospitalization from ischaemic hearth disease or stroke in male Swedish snuff users but an obvious excess risk in smokers. The study was based on a random sample of the Swedish population and adjusted for a number of confounders. A limitation was that tobacco use was recorded only at one point of time and participants may have changed their tobacco habits during follow-up.

WENNBERG *et al.* (142) confirmed the results of HAGLUND *et al.* (141). In a case-control study nested in the Northern Sweden MONICA study, they investigated the risk of first myocardial infarction and sudden cardiac death in male snuff users (525 cases and 1,798 matched references). No increased risk for myocardial infarction was found in male snuff users without a previous history of smoking. In snuff consumers with a former smoking history, the tendency detected towards an increased risk for myocardial infarction may have reflected the residual risk from former smoking. The hypothesis that the risk for sudden cardiac death is increased in snuff users was not supported by this study. However, the number of sudden cardiac death cases was as low as 93 and the results needed to be confirmed in a larger study.

In a follow-up of the Swedish Construction Workers Cohort in 2008, HERGENS *et al.* (143) found no increased overall risk of stroke in snus users compared to non-users of tobacco but a slightly increased risk of fatal ischemic stroke associated with current snuff use. The authors concluded that snuff use may elevate the risk of fatal stroke, particularly of fatal ischemic stroke.

In summary, the data of the studies in Sweden did not show a clearly increased risk of circulatory disease – including stroke – resulting from the use of Swedish snus.

In the U.S., ACCORTT and co-workers (96) observed no increased risk of cardiovascular disease mortality in smokeless tobacco consumers, males and females, after controlling for possible confounders.

A modest risk of cardiovascular disease associated with U.S. smokeless tobacco use was reported in 2006 by MUSHTAQ (144). No information was provided on which kind of smokeless tobacco was consumed by participants.

In 2007, HENLEY and co-workers (124) reported a significant slightly increased risk for all circulatory diseases in male U.S. smokeless tobacco consumers of 1.18 (95 % CI: 1.11–1.26) in the cohort of the U.S. Cancer Prevention Study No. I, and of 1.23 (95% CI: 1.09–1.39) in the cohort of the U.S. Cancer Prevention Study No. II. The type of smokeless tobacco used was not identified in CPS-I while a distinction was made between chewing tobacco and snuff consumption in CPS-II.

Evaluating the overall evidence for the association between smokeless tobacco use and all circulatory diseases (ischemic heart diseases, stroke) LEE (128) recognized that the RR of 1.25 (95% CI: 1.13–1.37) depended to a considerable extent on the two large U.S. studies, CPS- I and CPS-II. Together, these studies provide 76% of all studies cases for ischemic heart disease and 90% for stroke. LEE identified a number of confounders, which may have influenced the outcome of the two studies.

ASPLUND (145) reviewed the published literature concerning smokeless tobacco use in North America and Scandinavia (mainly snuff and chewing tobacco) and cardiovascular disease. Smokeless tobacco causes an immediate increase of heart rate and blood pressure, but regular users did not show permanent changes. Users of smokeless tobacco usually do not have the biochemical stigmata that regular smokers have. Concerning myocardial infarction and stroke as endpoints the evaluation did not show an increased risk in male snuff users.

In 2007, LEE (128) examined the evidence for associations of smokeless tobacco use and circulatory diseases in Western populations by meta-analysis, using the same approach as WEITKUNAT *et al.* (98). Attention was restricted to chewing tobacco and snuff use in Western populations (in practice, this meant U.S. and Sweden). The evaluation was focused on evidence from epidemiological

studies linking the use of smokeless tobacco to mortality from, or prevalence and onset of, ischemic heart disease, acute myocardial infarction, stroke or all circulatory diseases. The effect of smokeless tobacco on other risk factors for circulatory diseases was investigated qualitatively. According to Lee the earlier review by CRITCHLEY and UNAL (146) concluding that "there may be an association between smokeless tobacco use and cardiovascular disease" was limited because it did not include meta-analyses and studies on stroke. Only three (132, 137, 138) of the eight epidemiological studies available to Lee (96, 124, 132, 134, 137, 138, 140) were included in CRITCHLEY and UNAL's review. LEE reported that smokeless tobacco use was associated with slightly increased risks of heart disease (RR = 1.12; 95% CI: 0.99–1.27), stroke (RR = 1.42; 95% CI: 1.29–1.52) and circulatory disease (RR = 1.25; 95% CI: 1.14–1.37) compared to never-smokers. The increase mainly derived from two large U.S. studies, CPS-I and CPS-II (124). The Swedish studies (132, 134, 137, 138, 139, 149) provided little evidence of a risk increase for heart diseases or stroke in snus users. Regarding diabetes, increased blood pressure and other risk factors, evidence for an association with smokeless tobacco use was only qualitatively reviewed by LEE, with results from clinical studies also considered. No clear relationship with diabetes was seen. In the U.S., an acute blood pressure rise following smokeless tobacco use was consistently reported. In Sweden, though one study reported that snuff acutely increased blood pressure (147) and two linked snuff to Raynaud-type symptoms (148, 149), the overall evidence for an effect was inconclusive. Swedish studies generally showed no chronic effect of snuff on blood pressure or other risk factors for circulatory disease and stroke.

In 2009, BOFFETTA and STRAIF (150) conducted a meta-analysis of the association between smokeless tobacco use and the risks of myocardial infarction and stroke. The study was restricted to users of smokeless tobacco products from Sweden and North America. Eleven studies were included in the meta-analysis, eight from Sweden and three from the United States. The results of this meta-analysis did not differ substantially from those obtained by LEE (128) although BOFFETTA and STRAIF included in their analysis five studies from Sweden published after 2007 (135, 136, 141, 142, 143). An overall relative risk for stroke of 1.40 (95% CI: 1.28–1.54) and for fatal myocardial infarction of 1.13 (95% CI: 1.06–1.21) compared to non-tobacco users was found. This was not surprising. Again, the overall evidence depended particularly on the two large U.S. studies, CPS-I and CPS-II (124), which together provided 85% of all cases of myocardial infarction and 89% of all cases of stroke in the review of BOFFETTA and STRAIF.

The two CPS-based studies by HENLEY *et al.* (124) deserve another look because of their size and useful design. LEE (128) pointed out that CPS-I and CPS-II data were adjusted for a wide range of confounding variables but certain aspects required comment. The questions on smokeless tobacco use were asked in 1959 (CPS-I) and 1982 (CPS-II). It is questionable how relevant the products consumed at that time are to today´s smokeless tobacco products. The question used in CPS-I "Do you chew tobacco or use snuff" with answers recorded as "Never", "Occasionally" or "Regularly" are imprecise. No specific provision was made for former use. For calculating a dose-response relationship – a prerequisite for demonstrating causality – the recorded answers were not suitable. Consequently, no indication of dose-response relationships between smokeless tobacco consumption and ischemic hearth disease and stroke were found. There are comments by HENLEY *et al.* (124) reflecting the generally poorer lifestyle characteristics of smokeless tobacco users compared to non-tobacco users. Therefore, the possibility of residual confounders could not be excluded.

BOFFETTA and STRAIF (150) concluded that there was an association between the use of smokeless tobacco products and the risk of fatal myocardial infarction and fatal stroke, which is not readily explained by chance. On the contrary, LEE (128) concluded from nearly the same set of studies that "any circulatory disease (including fatal ischemic heart infarct and stroke) from smokeless tobacco appears to be substantially less than from smoking, and no clear risk from Swedish snuff was seen".

Finally, regarding a rather rare circulatory event, KOSKINEN and BLOMSTEDT (151) found no increased risk for subarachnoid hemorrhage in snuff users. They concluded that nicotine was unlikely to be solely responsible for the rupture of cerebral aneurisms as smoking was a risk factor for this health condition.

The association between smokeless tobacco use and cardiovascular disease and stroke was reviewed by ASPLUND (145), CRITCHLEY and UNAL (146), ROTH *et al.* (80), BROADSTOCK (81), LEE (128) and BOFFETTA and STRAIF (150).

h) Inflammatory bowel disease, metabolic syndrome, diabetes, malignant lymphoma and amyotrophic lateral sclerosis: No association was found between Swedish moist snuff consumption and inflammatory bowel disease (152), diabetes (153) and malignant lymphomas (154). LEE (128) concluded in a review that there was no clear evidence of any effect on diabetes of snuff as used in Sweden.

In 2006, NORBERG *et al.* (155) examined the contribution of Swedish moist snuff to the so-called metabolic syndrome in a prospective study. An association was found between high snus consumption and the metabolic syndrome. Consequently, an increased risk of cardiovascular diseases and diabetes was suspected.

Two years later, a population-based cross-sectional study was undertaken by WÄNDELL *et al.* (156) in Stockholm County with 1,859 men, aged 60 years. No significant association between any use of tobacco and the metabolic syndrome or diabetes was observed though an association between snuff use and the risk of diabetes was not ruled out.

FANG-FANG *et al.* (157) investigated smoking and snuff dipping and the risk of amyotrophic lateral sclerosis among the cohort of the Swedish construction workers. No increased risk was detected.

i) Pregnancy outcome: In a cohort study, ENGLAND *et al.* (158) investigated adverse health effects in pregnant women exposed to Swedish moist snuff. Groups of snuff users (n = 789) and cigarette smokers (n = 11,249) were compared to non-tobacco users (n = 11,495). Tobacco exposure was reported by the women themselves and not

validated. There was a control for several confounders, such as maternal age, parity, body mass index, infant gender, etc. However, there was no control for other important confounders, including education, nutrition, alcohol and drug consumption and socio-economic status.
With respect to pregnancy outcome compared to non-tobacco using mothers, Swedish moist snuff was associated with reduced infant birth weight, an increased risk for both pre-term delivery and – in contrast to smoking – pre-eclampsia. The study was limited by the way tobacco exposure was recorded, possible reporting biases and the shortcoming of incomplete confounder control. In particular, self-reporting of tobacco use by pregnant women is very susceptible for reporting bias. Pregnant women tend to under-report smoking to avoid the stigmatization associated with smoking during pregnancy. For clarification additional studies, specifically case-control studies are called for.
The association between smokeless tobacco use and effects on pregnancy outcome was reviewed by BROADSTOCK (81).

DISCUSSION

The presence of carcinogens in smokeless tobaccos, especially of the TSNAs, NNN and NNK, is the major reason for examining very carefully whether an increased risk for cancer is observed in smokeless tobacco consumers (53, 57, 159). It was shown in animal models (rats) that chronic treatment of the buccal mucosa with pure NNN and NNK resulted in tumor formation at the site of exposure. However, when applying these TSNAs together with an aqueous extract of smokeless tobacco the number of tumors was reduced. No tumors were induced with the extract alone (160). In a second study, NNK and its metabolite NNAL were administrated to male rats for lifetime in the drinking water. A dose dependent incidence of tumors of the lungs and the exocrine pancreas tumors was observed with both nitrosamines (161).
The uptake of TSNAs by smokeless tobacco consumers was examined in a number of studies. HECHT *et al.* (162) investigated the uptake of NNK from U.S. moist snuff. They analyzed the amounts of NNK in the tobacco before and after use and in the smoker's saliva. The daily uptake of NNK was estimated to be around 6 µg. In comparison, in the late 70s of the last century a daily uptake of 24 to 46 µg TSNAs was calculated for consumers of 10 grams of U.S. moist snuff per day (54) – equivalent to at least 10 to 12 µg NNK. In their study, HECHT *et al.* also measured total urinary NNAL excretion, i.e. the metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol and its glucuronide, and found that 14–17% of the NNK taken up from the snuff were converted to NNAL.
In 1996, a relationship between the level of excreted urinary NNK metabolites (total NNAL) and the incidence of oral leukoplakia in smokeless tobacco users could be shown by HECHT's group (163).
Comparable exposures to NNK were reported by HECHT *et al.* (164) in traditional U.S. smokeless tobacco users and cigarette smokers. NNK exposure was assessed by means of NNAL excretion in the urine of groups of male persons, who wanted to quit smoking or the use of smokeless tobacco. HATSUKAMI *et al.* (165) found that switching from a typical U.S. smokeless tobacco to Swedish snus (a low nitrosamine snuff) reduced urinary total NNAL excretion by about 56% to levels lower than seen in smokers. HECHT *et al.*, however, concluded that Swedish snus was not a "low nitrosamine" product and NNK exposure in smokeless tobacco users presented an unacceptable risk. Snus use should not be encouraged. Use of smokeless tobacco was not a safe substitute for smoking.
In our opinion, this statement is missing the point. HECHT *et al.* create the impression that NNK and NNN are the most important components responsible for cancer both in tobacco smoke and especially in smokeless tobacco (164). If this was true the risk for certain cancers in cigarette smokers and users of modern smokeless tobacco should be comparable, especially as nicotine uptake in both groups of consumers is at similar levels. As shown in many studies and discussed above in detail the cancer risk associated with today´s U.S. and European smokeless tobacco is at least 90% less compared to cigarette smoking. The statement "smokeless tobacco is not a safe substitute for smoking" raises the question what a safe substitute or alternative might be. Long-term nicotine replacement therapy is obviously accepted only by a minority of cigarette smokers (166, 167). Undesirable side effects of pharmaceutical smoking cessation aids, such as the antidepressants bupropion and varencine, cannot be excluded (168). Therefore, a certain health risk remains and these smoking alternatives also cannot be regarded as "safe" in the strict sense of the word.
Modern smokeless tobacco appears to be a product much less risky than cigarettes and, therefore, an alternative to the awesome "quit or die" for persons who are not willing to abstain from tobacco consumption. Snus, as "low nitrosamine" smokeless tobacco, shows less genotoxic potential than some other moist snuff types (169). This fact is very much in line with the considerably reduced cancer risk in snus users.
Early observations in animals by HECHT and co-workers, the historically high TSNA levels in U.S. moist and dry snuffs (no longer realistic today) and epidemiological studies from the U.S. and Asia showing increased cancer risks in smokeless tobacco users were the main reasons for IARC in 1987 (52) to conclude that for smokeless tobacco products there was "sufficient evidence for carcinogenicity to humans" (Group 1). Consequently, the sale of oral snuffs is no longer legal in the member states of the European Community except Sweden (24). TSNA levels have decreased dramatically during the last decades due to technical measures in tobacco cultivation and processing and in the ways smokeless tobaccos are manufactured and stored. Nevertheless, the classification of smokeless tobaccos was confirmed by IARC in 2007 (53) as being "carcinogenic to humans" (Group 1).
The reduced tumor induction in experimental animals by NNN/NNK in the presence of aqueous smokeless tobacco extracts – as mentioned above – deserves some reflection. According to RODU and JANSSON (7) this may be explained by the fact that the extracts contain substances, which inhibit the carcinogenic potency of TSNAs. BROWN and co-workers investigated the contribution of NNK to the biological activity of cigarette smoke condensate in A/J-mice. They demonstrated that the mutagenicity and carcino-

genicity of NNK were inhibited by nicotine and cotinine as well as other unidentified components in tobacco smoke (170). As nicotine is an abundant component in smokeless tobaccos it can be assumed that an inhibition can be brought about also by smokeless tobacco extracts.

In addition to other carotenes, luteine, ß-carotene, neoxanthine and violaxanthine are present in tobacco leaves (35, 171). There is some evidence that ß-carotene inhibits the formation of cancerous lesions (172) and also induces the regression of about 50% of oral leukoplakias, as observed in clinical studies (173).

Phenolic compounds are natural tobacco components, which probably represent the major anti-oxidants in tobacco (35, 174, 175). Polyphenols from black and green teas and from cruciferous vegetables exert an inhibitory effect on lung tumorigenesis provoked by NNK in animals (176, 177).

In 2000, RODU and OU (178) published a study on the anti-oxidant properties of tobacco products available in the U.S. and determined their content of total phenols. Ten moist snuff brands, two chewing tobaccos, two pelletized leaf tobacco products and the filling tobacco of two American blend cigarettes were investigated. Considerable differences were observed between these tobacco products. A strong correlation was found between the anti-oxidant properties and the content of total phenols. In general, the anti-oxidant properties of tobacco products were similar to those reported for fruit and vegetables (179). Possible explanations for the differences in the anti-oxidant properties between different tobaccos may be cultivation techniques, curing methods and the kind of fermentation. The antioxidant activity may also be influenced by additives to the tobacco, such as flavorings and casings. By modifying these factors the anti-oxidants levels in tobacco and, consequently, the tumorigenicity of TSNAs could be influenced (180).

The unequivocal confirmation of the cancer risk reduction by carotenes, poly-phenols and other anti-oxidants in smokeless tobacco consumers compared to smokers is still missing. The potential influence of these compounds may be used as a solid working hypothesis, which will be accepted or rejected depending on the results of further investigations. As pointed out by Rodu and Jansson, studies are needed to determine the extent to which anti-oxidants in tobaccos are available to, and can be absorbed by, smokeless tobacco consumers (7). If the hypothesis of cancer risk reduction by anti-oxidants in tobacco users is accepted and sufficient bioavailability of these substances to consumers is demonstrated, new ways for modifying tobacco products towards "less risky" are open. They can be followed by breeding and agricultural approaches, by genetic engineering, by techniques of tobacco curing and fermentation and – last not least – by the addition of suitable ingredients in product manufacturing.

The voluntary Gothia Tek Standard (12) defines maximum levels for several toxic substances in Swedish moist snuff (snus). The immediate effects of this regulation on reducing the health risks for snus users have not yet been demonstrated though the epidemiological evidence is rather suggestive. Many epidemiological studies have shown that the health risk from snus is smaller than that associated with other types of snuff. It is obviously a benefit for snus users that the levels of toxic substances and contaminants are being kept as low as possible. Which compounds are specifically involved has not yet been clearly shown. In any case, the information is helpful for breeding suitable tobaccos and for the techniques used in tobacco processing. These thoughts are equally important for smokeless tobaccos and for the development of new smoking products.

Comparing analytical data for smokeless tobacco products marketed in the U.S. and Sweden in the early eighties of the last century and today shows convincingly that the reduction of the potentially carcinogenic TSNAs was possible (67). Changes in the fertilization methods during tobacco cultivation, modification of the curing process and exact control – or even abandonment – of fermentation in combination with pasteurization were the measures for achieving this goal (47, 48, 49, 50, 65, 174, 181).

The importance of controlling the agents of concern in smokeless tobacco was emphasized by SAVITZ *et al.* (182) as a prerequisite for implementing a harm reduction strategy by promoting a product (smokeless tobacco) that still has adverse health consequences as a substitute for one (cigarettes) that has more severe adverse health consequences.

The toxic components regulated by the Gothia Tek Standard can effectively be controlled in tobacco products. On the one hand, BaP is an avoidable airborne contaminant of tobacco. On the other, unsuitable curing processes may be the source for this carcinogen and other PAHs on tobacco, especially on fire-cured tobacco. The origins of polonium-210 on tobacco are certain phosphate fertilizers (183). The levels of metals, such as cadmium, arsenic, chromium, lead and mercury, depend on the content of these metals in the soil, which the tobacco has been cultivated on. Reduction of the levels of these chemicals in tobacco appears to be possible (184).

In general, the results of most epidemiological studies on smokeless tobacco use and health risks are – often considerably – influenced by potential confounders, such tobacco smoking, exposures in working places, diet, alcohol consumption, personal life style and family history of cancer and cardiovascular diseases. Information on tobacco use was often collected by questionnaires or telephone interviews. Especially in prospective studies, the habit and kind of tobacco use (cigarette, pipe, chewing or dipping) is often recorded only at the beginning; checks of the habit during follow-up are rarely reported. That is also true for consumption details, such as grams consumed per day.

The wording "long time smokeless tobacco user" is imprecise and, therefore, not helpful for interpreting and evaluating epidemiological findings. Consequently, dose-response relationships are missing in nearly all studies. An exact – or at least sufficient – characterization of the type of smokeless tobacco is also important for interpreting study results. Generally, the exact validation of this kind of information – e.g., by bio-markers – was not done for technical reasons. Bias and misclassification are quite possible. Problems arise if in non-fatal cases the source of information are questionnaires answered by the cases themselves, whereas in fatal cases the answers are predominately supplied by the next of kin; this is for instance

the case in the studies of HERGENS (135, 143). Information bias in the data is quite possible.

Many studies did not control for confounding by alcohol consumption, by active smoking or – in some instances – for body mass and family disposition for specific diseases. In evaluating the relationship between smokeless tobacco use and the various cancers many of the studies did not clearly define the specific anatomic features studied and the examined histological cell type.

Smokeless tobacco products are different and their content of toxic substances, especially TSNAs, has changed considerably over time (67, 185).

As shown by RODU and JANSSON (7), the levels of total TSNAs in U.S. moist oral snuff vary by a factor of more than two (4.5–12.3 ppm) and are quite different from the levels in Swedish moist snuff (2.0–2.2 ppm). As the TSNA content is assumed to be very relevant for the magnitude of the health risk associated with smokeless tobacco (51, 53), the snuff consumed by the population at risk should be characterized in great detail to allow the sound evaluation of all health relevant data.

The question whether and to which extent the use of smokeless tobacco may influence an existing smoking habit is an important one. On the one side, it may be a cessation aid for smokers who are not willing to resign from nicotine or use pharmaceutical nicotine containing precipitates. On the other side, however, it may be a gateway for smoking. These questions were discussed heavily in recent years.

It is a fact that for decades men in Sweden have smoked at far lower rates than those in comparable countries. In northern Sweden, daily smoking declined from 19% in 1986 to 11% in 1999. Total tobacco consumption remained constant in men as well as in women (186, 187). In 2004, the prevalence of smoking was 9% in all men and only 3% in men with an age of 25–35 years. Between 1986 and 2004 the prevalence of exclusive snus use increased from 18% to 27 %. The decrease of smoking was observed for the first time in women in 2004, associated with an increase of snus use (188).

GILLJAM and GALANTI (189) reported in a study from Sweden, where current smoking status was investigated in relation to snus use, that male smokers increased their overall chances of abstinence by using snus by 50% (OR = 1.54; $p < 0.05$). Nearly one-third of ex-smokers in the sample consumed snus regularly. Current cigarette smokers who made use of snus smoked on average fewer cigarettes per day than non-users of snus. The results of this study indicate that snus reduces the overall cigarette consumption among men.

In 2006, data from a nationwide representative sample of adults in Sweden suggested that smoking in combination with smokeless tobacco use was rare (190). In men, only 2% were smoking and using snuff on a daily basis. In women, dual tobacco consumption was even less frequent. However, in the U.S. smoking combined with smokeless tobacco use is not uncommon among men. In 2002, 58% of all male smokeless tobacco consumers were also smokers (191).

HERGENS *et al.* (143) reported that smokers, who also used snuff, smoked less. LUNDQUIST *et al.* (192) studied the long-term pattern of tobacco use over a 10-year period among middle-aged men and women in Northern Sweden. Between 1994 and 2004, smoking prevalence decreased from 22.3% to 15.6% among women and from 18.7% to 12.5% among men. The majority of middle-aged Swedish men and women quit smoking during the observation period without changing to snus. The use of snus increased from 3.1% to 6.0% among women and from 24.6%to 26.3% among men. The percentage of persons who indulged in both habits (cigarettes and snus) was stable (at 0.5–0.8 % among women and around 3.5% among men).

According to FURBERG *et al.* (193) cigarette smoking is more prevalent among Swedish women while snus use is more widespread among men. Among men, who reported using both cigarettes and snus during their lifetime, it was more common to quit cigarettes and currently use snus than to quit snus and currently use cigarettes. Once snus use was initiated, more men continued using snus rather than quitting tobacco completely.

In a cross sectional study in southern Sweden, LINDSTRÖM (194) examined the strategies used to support smoking cessation among quitters. In men, snus was commonly used as an alternative to cigarette smoking but not in women.

In 2008, GALANTI *et al.* (195) investigated the question whether the use of smokeless tobacco facilitated the transition to cigarette smoking and/or to prolonged tobacco use in adolescents. Data from a cohort of 2,938 Swedish adolescents were analyzed with follow-up assessments of tobacco use between the ages of 11 and 18 years. Adolescents who initiated tobacco use with cigarettes had a non-significantly increased probability (OR = 1.42; 95 % CI: 0.98–2.10) to end up as current smokers compared with snus starters. The proportion of adolescent smoking prevalence attributable to the potential induction effect of snus was assumed to be small.

In a middle-aged Swedish population LUNDQVIST *et al.* (192) found in 2009 that switching to snuff might have helped men and women to quit smoking.

LUND *et al.* (196) investigated and compared the prevalence of smoking and snuff use amongst Norwegian students and non-students. They identified a high proportion of former cigarette smokers among male snuff users, which indicated that snuff may affect the prevalence and frequency of smoking in a population.

The results found in Sweden are not fully in accordance with those from the U.S. TOMAR (191) concluded from data obtained in an examination of the interdependence of using snuff and quitting smoking that U.S. men commonly switched from snuff use to smoking. Some smokers may have used snuff to supplement their nicotine intake. Smokers who also used snuff were more likely than non-users to try to quit smoking but tended to have less success. In 2009, ZHU *et al.* (197) were also not able to confirm the Swedish results in the United States.

COBB *et al.* (198) conducted a laboratory study with twenty-eight overnight abstinent cigarette smokers and found that smokeless tobacco products delivered less nicotine than cigarettes and failed to suppress smoking abstinence symptoms. They concluded that these non-combustible tobacco products may not be suitable for a harm reduction strategy in U.S. smokers. In our opinion, this unrealistic laboratory study with participants who did not really intend to quit smoking is not suitable for evaluating smokeless tobacco products – especially "Potential

Reduced Exposure Products“ in connection with harm reduction strategies as discussed by the U.S. Institute of Medicine in 2001 (199).

To avoid any misinterpretation concerning less harmful tobacco products the term PREP (“Potential Reduced Exposure Product”) was clearly defined in 2001 by the U.S. Institute of Medicine (199). PREPs show decreased emission of some toxicants, or group of toxicants, compared to conventional tobacco products. These products could, therefore, potentially result in reduced exposure to toxicants. “Potentially” is used because, whether exposure to tobacco toxicants is in fact reduced, depends on the consumer´s behavior, such as frequency and intensity of use. Reduced exposure, however, does not necessarily assure reduced risk to the user or reduced harm to the population.

According to this definition smokeless tobacco products are in principle “PREPs” when compared to traditional smoking products. Qualitatively, smokers are exposed to the same kind of tobacco components as users of smokeless tobacco, but additionally to the substances generated by the burning and pyrolysis of tobacco. Some of them are acutely irritating to the breathing system, others are toxic, carcinogenic or mutagenic. The exposure of consumers of smokeless tobacco in the European countries and the USA to substances generated by burning tobacco is very low and may be neglected. As shown by various epidemiological studies the overall cancer risk and the risks of other smoking associated diseases for users of modern smokeless tobaccos is very considerably lower than the risk for smokers. The risks for Swedish snus users are particularly low. The Royal College of Physicians of London concluded in 2002 that, as a way of using nicotine, smokeless tobacco is 10 to 1000 times less hazardous than smoking, depending on the product (200).

Evaluation of the present knowledge on health risks of users of modern types of smokeless tobacco leads to the conclusion that these tobacco products meet the requirements of PREPs as defined by the U.S. Institute of Medicine (199). Especially, the use of Swedish moist snuff and some nasal snuffs may be a “less harmful” alternative for nicotine dependent cigarette smokers. It seems, therefore, necessary to reconsider the sales restrictions of Swedish moist snuff in the EU Member States, which are obviously based on outdated information.

The EU policy on smokeless tobacco was recently discussed and criticized by Bates and co-authors (201). They pointed out that smokeless tobacco was not harmless. However, some products, in particular Swedish moist snuff (snus), were considerably less harmful than others. Current EU regulations ban Swedish moist snuff (except in Sweden) but permit the sale of chewing tobacco. The highly toxic Indian varieties of smokeless tobaccos are also allowed on the European market. Toxicological and epidemiological data indicate that Swedish moist snuff is at least 90% less hazardous than cigarette smoking. This was confirmed by an expert panel in 2004 (202). In comparison to smoking, the experts perceived an at least 90% reduction in the relative risk of low-nitrosamine smokeless tobacco use. Data also indicated that in Sweden the high use of snus contributed to the low prevalence of cigarette smoking in men and made an important contribution to the low rates of Swedish tobacco related mortality (186).

Recently, RODU and COLE (203) described the mortality attributable to smoking in the EU and the change that would result if all EU countries had the smoking and smokeless tobacco use prevalence of Sweden. Almost 500,000 smoking attributable deaths occur annually among men in the EU; about 200,000 would be avoided in men at Swedish smoking rates. In contrast, only 1,100 of the 105,000 deaths attributed to smoking would be avoided if women in the EU smoked at Swedish rates. In 2004, the prevalence of tobacco use among Swedish men (smokeless tobacco use, predominately snus: 20%, smoking: 19%) was the same as the prevalence of smoking among men throughout the EU (40%). The number of Swedish smoking women (25%) was comparable to the European average (26%). Therefore, it must be concluded that the low smoking-related mortality among Swedish men is due to their use of Swedish moist snuff.

BATES *et al.* (201) support the revocation of the ban of Swedish moist snuff, one of the least harmful forms of smokeless tobaccos throughout the EU, by a regulatory framework applying to all smokeless tobacco products for offering a less hazardous nicotine delivery system to tobacco consumers. The statements made in 2003 by the U.S. Surgeon General before a Congress Committee: “No matter what you may hear today or read in press reports later, I cannot conclude that the use of any tobacco product is a safer alternative to smoking” and “There is no significant scientific evidence that suggests smokeless tobacco is a safer alternative to cigarettes” (204) are authoritarian and mislead the public and consumers. This kind of attitude prevents an effective approach for controlling smokers’ risks, inhibits the reduction or elimination of the burden of environmental tobacco smoke and does not respect smokers’ rights of free choice of their options for harm reduction.

According to BATES *et al.* (201), a precondition for lifting the sales ban in the EU are strict legal regulations for all types of smokeless tobacco. The Tobacco Advisory Group of the Royal of the Royal College of Physicians (205) asks for similar legislation because specific types of smokeless tobacco should be offered for ethical reasons to tobacco consumers for harm reduction.

In 2006, public health implications of smokeless tobacco use as a harm reduction strategy were discussed by SAVITZ and co-workers (182). Although several open questions were waiting to be answered about smokeless tobaccos, they concluded that smokeless tobacco products, particularly those low in nitrosamine content, would represent a beneficial alternative for those smokers, who are unable or not willing to quit. Equally, modern smokeless tobacco products were recommended for tobacco/smoking harm reduction by RODU and GODSHALL (206).

These considerations, however, are not in line with the position of the International Agency on Research on Cancer (IARC) in Lyon, which confirmed smokeless tobacco as Group 1 carcinogen (“carcinogenic to humans“) in 2007 (53). As discussed earlier, the all-out classification as “carcinogenic to humans” without any regard to the type and quality of the smokeless tobaccos under assessment is flat, misleading and not helpful in the efforts of reducing the harm connected with tobacco consumption in general.

In 2007, the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) of the European Com-

mission prepared a preliminary report on the health effects of smokeless tobacco products (207). This report was intended to form the scientific basis for possible new regulations for smokeless tobacco in the EU and was not solely focused on Swedish moist snuff. The chapters on chemical composition and health risks, especially cancer risks, are nearly identical with the corresponding chapters of the IARC report (53) and represent a scientifically valid overview on the association between smokeless tobacco use and health risks. In a public consultation several conclusions of the preliminary report – which do not always seem to be in accordance with the evidence shown in the different chapters – were discussed intensely: the composition, health effects and addictiveness of smokeless tobacco products, the question whether their use may be a gateway into or out of smoking and the possibility of transferring the experience with Swedish moist snuff (snus) to other countries. Independent scientists as well as scientists working in the tobacco industry, health politicians and representatives of anti-tobacco NGOs were invited to participate in the consultation. Partly, the conclusions in the draft report were heavily criticized for scientific reasons. However, nearly all health politicians and representatives of NGOs agreed. The final report was published in 2008 but most of the critics were ignored (208). The report pointed out that the use of smokeless tobacco carries risks for cancer but for those who substitute smoking by smokeless tobacco use the benefits would outweigh the risks.

In spite of the classification of smokeless tobacco by the IARC (53), current smokers who switch to using snus rather than continuing to smoke may achieve substantial health gains. This was shown in a modeling study by GARTNER and co-workers in 2007 (209). The authors concluded that it was unlikely that these health gains would be offset by adverse health effects of snus use among current smokers, who would have otherwise quit all tobacco use, and among people, who had never used tobacco and might now become snus users because the product was easily available. The actual size of the probable population-health benefit would depend on the relative adoption rates of Swedish moist snuff by the smokers and non-tobacco users, who changed their habit. The paper of GARTNER *et al.* was heavily criticized in a "Letter to the Editor" by MCKEE, GILMORE and M. LAMBE (210). They assumed that the availability of snus in smoke-free environments would probably encourage smokers to remain addicted to nicotine, retaining them as cigarette buyers and reducing the health effects of smoke-free legislation. A dual use of snus and cigarettes was to be expected. In addition, the health benefits of snus would be lower because the model used by Gartner and her colleagues was questionable. Snus clearly was no necessary component for tobacco control. The basis of this critique is the guiding principle of parts of the "Tobacco Control Community" that smokers should quit or die. In their response, GARTNER *et al.* (211) pointed out that the dual use of cigarettes and snus was without doubt a step towards harm reduction and defended the model used in their study.

It must, however, be pointed out that smoking cigarettes, cigars and other tobacco products is not simply a habit of nicotine up-take. The taste and aroma of tobacco smoke, the handling of the smoking articles and, last but not least, the social component are important factors for maintaining the smoking habit. Therefore, it is to be expected that only part of cigarette smokers would switch to smokeless tobacco. This would certainly be a major step forward in reducing tobacco related diseases. Equally important is the development and marketing of cigarettes, which can really be regarded as PREPs, for smokers not willing or able to change their habit. A guideline for the evaluation and regulation of such products was outlined by the U.S. Institute of Medicine in 2001 (199). We are fully in agreement with the statement of BRITTON and EDWARDS (212): "We believe that the absence of effective harm reduction options for smokers is perverse, unjust, and acts against the rights and best interests of smokers and the public health".

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