Report of the Working Group on Tobacco Additives

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1. Mandate

The Collegiate Board of Directors of Anvisa, held meetings, respectively, on October 02nd 2013 and December 19th 2013, when it was decided and the Director General of Anvisa made it public, the creation of a Working Group mandated to assess a list of additives used in tobacco products, as listed in annex to IN 06/2013.

According to Edit 1.980/2013 the Working Group is mandated to:

I- Attend meetings and events related to its work;
II- Assess the additives used in tobacco products, as listed in IN 06/2013;
III- Make a report on the use of additives temporarily approved by IN 06/2013;
IV- Assist in defining the claimed technological functions for these additives.

2. Background

The Resolution of the Collegiate Board of Directors of Anvisa, RDC 14/2012, was published on March 15th, 2012. Brazil (Resolution RDC ANVISA Nº 14, March 15, 2012) bans the use of most additives in all tobacco products. In this resolution, an additive is defined as *"any substance or compound that is not tobacco or water, used in the processing of tobacco leaf and reconstituted tobacco, in the manufacture and packaging of a tobacco product, including sugars, sweeteners, flavouring agents and (ameliorants)".* Regarding flavour, article 6 in this resolution describes that the following types of additives are banned: flavourings and ameliorants (included those classified by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and FEMA), and related processing aids; fruit and vegetable products; honey, molasses, sweeteners (except sugar, only to replace the content lost in the curing process of tobacco leaves); seasonings, herbs and spices.

One of the main objectives of this Resolution was to decrease the attractiveness of tobacco products. One of the provisions of RDC 14/2012 allowed the tobacco industry to submit requests to retain the use of additives, so long as those additives did not change the smell and taste of tobacco products.

On July 16th, 2012, the Brazilian Association of Tobacco Industry (Abifumo) submitted a request to Anvisa to approve the use of 145 additives. After more than a year of discussions and the analysis of the documents submitted, Anvisa's Tobacco Control Department (GGTAB) submitted a Technical Report to the Board of Directors, recommending that none of the additives requested by Abifumo should be allowed.

On August 26th, 2013, the Board of Directors published the Normative Instruction 06/2013, which allowed the use of 121 additives by industry for a period of one year. During this one-year period, Anvisa determined that these 121 additives should be evaluated by an independent expert group with respect to the Resolution.

On December 24th, 2013, the Anvisa's Board of Directors published Edit 1.980/2013, which established the Working Group on Tobacco Additives (WG).

On July 7th, 2014, Abifumo submitted material for the WG to consider in its review.

3. Methodology

A preliminary meeting of the WG was held at the INCQS-Fiocruz in Rio de Janeiro on April 16th, 2014. A second meeting was held in Brasilia-DF on June 4th-5th, 2014. The third and final meeting was also held at Fiocruz, on August 12th-14th, 2014. Although the three international members of the WG contributed to the work of the WG, they were only able to attend the third meeting.

In order to achieve its objectives, the WG determined that it was necessary to evaluate tobacco additives with respect to three aspects: (1) toxicity, (2) addictiveness, and (3) attractiveness. Because IN 06/2013 was based on RDC 14/2012, the WG determined that it was necessary to consider a broader set of additives beyond the 121 listed in IN 06/2013.

In addition, on July 21st, 2014, the members of the WG received a set of documents that had been submitted by Abifumo, the Association of Brazilian Tobacco Companies, dated July 7th, 2014. The WG thus reviewed these documents in the preparation of this report.

At the August 12-14, 2014 meeting, the WG decided to prepare this report in English. If an official translation to Portuguese is deemed to be necessary, this report shall be subjected to review by the Brazilian members of the WG.

B. Statement of General Principles

1. Definition of Additives

Natural tobacco consists of some 2,000 to 3,000 components. During the manufacturing process of tobacco products, manufacturers also use additives, including flavours. Modern American cigarette tobacco contains around 10 per cent additives by weight, such as sugars, menthol, moisturisers, cocoa, and liquorice. In the scientific literature, it is generally stated that over 600 ingredients are added to tobacco products.

Many additives are also present in natural tobacco or the resulting smoke. In principle, for taste and other effects, it does not make a difference whether a component is added or present naturally in tobacco or smoke. Therefore, from a scientific point of view, restricting the regulation of tobacco products only to those substances that are added may be considered a partial product regulation because other components such as those naturally present in tobacco are not taken into account. From a public health perspective, limiting product regulation in this way hinders the ability of the regulator to evaluate and, if deemed necessary, to restrict or ban substances that would be a part of the tobacco plant itself if such substances met the criteria of toxicity, addictiveness, and attractiveness. Being free to assess ALL substances, whether or not present in the tobacco plant itself, would provide regulators with a stronger mandate to reduce the harm of tobacco products.

This issue is recognised by the Partial Guidelines for Implementation of Articles 9 and 10 of the WHO Framework Convention on Tobacco Control (WHO FCTC), that describe *Regulation of the contents of tobacco products and Regulation of tobacco product disclosures.* Regarding contents regulation, it is stated that “contents” means “constituents” with respect to processed tobacco, and “ingredients” with respect to tobacco products. The definition used for ingredients is: `*Ingredients include tobacco, components (e.g. paper, filter), including materials used to manufacture those components, additives, processing aids, residual substances found in tobacco (following storage and processing), and substances that migrate from the packaging material into the product (contaminants are not part of the ingredients).*` Thus, the definition of ingredients is broader, consisting of tobacco, additives, and other substances that become incorporated into the tobacco product.

As indicated above, Brazil (Resolution RDC ANVISA Nº 14, March 15, 2012; hereafter referred to as “RDC 14/2012” or “the resolution”) bans the use of most additives in all tobacco products. Regarding flavour, Article 6 of the resolution states that the following types of additives are banned: flavourings and ameliorants (included those classified by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and FEMA), and related processing aids; fruit and vegetable products; seasonings, herbs and spices; honey, molasses, and sweeteners.

In Article 7 of the resolution, there was a list of exceptions to the ban. One notable exception was sugars (defined as “monosaccharides and disaccharides, including the sucrose obtained from raw sugarcane juice…or from beets“), which were NOT banned so long as the level of sugar added did not exceed the amount lost in the curing process of tobacco leaves. Sugars are natural components of tobacco (Fox, 1993; Leffingwell, 1999), but the sugar content of tobacco types is highly variable, primarily depending on the method of curing. For instance, sugar levels of over 20 weight percent have been reported in Virginia tobacco, whereas levels in Burley are nearly zero. During the manufacturing process of a tobacco product, sugars and sweeteners are intentionally added to tobacco (Fowles & Bates, 2000; Leffingwell, 1999; Rodgman, 2002; Seeman, Laffoon, & Kassman, 2003), usually reported to serve as flavour/casing and humectant.

Article 7 of the resolution also listed the following exceptions to the ban: adhesives, binders, combustion agents, processing aids that are not for flavourings, pigments (or coloring agents), glycerol and propylene glycol, and potassium sorbate.

The definition of additive in RDC 14/2012 is very similar to the definition used in the SCENIHR report, Addictiveness and Attractiveness of Tobacco Additives, which is: "any substance that is added, except water, during the course of manufacture of a tobacco product, including preservatives, humectants, flavours, and processing aids."

The definition of additive in RDC 14/2012 is also very similar to the definition used in the European Tobacco Product Directive (2014/40/EU), which defines 'additive' as "a substance, other than tobacco, that is added to a tobacco product, a unit packet or to any outside packaging, whereas 'ingredient' means tobacco, an additive, as well as any substance or element present in a finished tobacco product or related products, including paper, filter, ink, capsules and adhesives."

2. Impact of Tobacco Additives on Public Health

a. Additives and Flavourings in Food vs. Tobacco

Food Additives

Food additive means any substance not normally consumed as a food by itself and not normally used as a typical ingredient of the food, whether or not it has nutritive value, the intentional addition of which to food for a technological (including organoleptic) purpose in the manufacture, processing, preparation, treatment, packing, packaging, transport or holding of such food results, or may be reasonably expected to result, (directly or indirectly) in it or its by-products becoming a component of or otherwise affecting the characteristics of such foods. The term does not include "contaminants" or substances added to food for maintaining or improving nutritional qualities (Codex Alimentarius Commission, FAO, http://www.fao.org/docrep/005/y2200e/y2200e07.htm).

Food Flavourings

Food flavourings are food additives used to give taste and/or smell (flavour) to food. "Flavour" is defined as "...the sum of those characteristics of any material taken in the mouth, perceived principally by the senses of taste and smell and also the general pain and tactile receptors in the mouth, as received and interpreted by the brain." A flavouring may be a single chemical entity, or a blend of chemicals of natural or synthetic origin (i.e., flavouring substances) whose primary purpose is to provide all or part of the particular flavour effect to any food or other product taken in the mouth (Hall & Merwin, 1981).

There are different types of flavourings, such as natural, natural-identical or artificial flavouring substances, flavouring preparations of plant or animal origin, and process flavourings which evolve flavour after heating and smoke flavourings (Article 1(2) of Directive 88/388/EEC).

As food additives, food flavourings may only be authorized if there is a technological need for their use, they do not mislead the consumer and present no hazard to the health of the consumer.

Use of Flavourings in Tobacco

Many of the flavouring compounds used for food have also been added to tobacco products for different purposes. Besides enhancing the taste of the tobacco product (thereby increasing its attractiveness), specific flavourings may perform other functions, as described in the SCENIHR report, which generally do not fit into the definition of flavourings. These include:

- ✓ reducing the harshness of tobacco smoke and the irritating effects of nicotine;
- ✓ reducing the acidity of the smoke, which may serve to increase nicotine absorption;
- ✓ producing local anaesthetic effects;
- ✓ producing bronchodilation (opening/broadening the airways) that would enable the smoker to inhale deeper, increasing the exposure to nicotine and other toxicants.

Safety of Flavourings

It should be noted at the beginning of this section that well-established procedures exist to assess the safety of flavourings for food. However, these procedures and the results of these procedures are applicable only for food flavourings and are not relevant for the safety assessment of flavourings or other additives for tobacco products that are inhaled. Moreover, some additives of tobacco products that are burned (e.g., cigarettes) are subjected to pyrolysis, and this creates the potential for combustion products that were not present in the original additives.

The safety assessment of flavourings for food uses has been performed by national and international scientific committees, such as the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-flav/en/).

JECFA is an international expert scientific committee that is administered jointly by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO). It regularly addresses the technical aspects of chemical additives and their safety in food. It also develops principles for the safety assessment of **chemicals in food** that are consistent with current thinking on risk assessment and take account of recent developments in toxicology and other relevant scientific areas such as microbiology, biotechnology, exposure assessment, and food chemistry including analytical chemistry.

JECFA advises the Codex Alimentarius Commission on food additives, contaminants and naturally occurring toxicants. Assessment of the exposure to food additives is performed taking into account dietary sources, based on information on known or anticipated human exposure to the proposed **additive to food** or toxicologically relevant components of the additive, and any other potential **dietary sources** (e.g. natural occurrence in food, non-additive use in food supplements, use as a nutrient, use as a flavouring, use as a food contact material, use in pharmaceuticals or cosmetic products) (World Health Organization & Nations, 2006).

To date, JECFA has evaluated more than thousands of food additives, several contaminants and naturally occurring toxicants, and the residues of hundreds of veterinary drugs. The Committee has also developed principles for the safety assessment of chemicals in food that are consistent with current thinking on risk assessment and take account recent developments in toxicology and other relevant scientific areas such as microbiology, biotechnology, exposure assessment, food chemistry including analytical chemistry and the assessment of maximum residue limits for veterinary drugs.

Food-grade flavouring compounds are, by definition, **not tested for inhalation**. It has been recognized that there are likely to be health implications resulting from inhalation of some flavours. Diacetyl (creamy, buttery taste), for example, may cause adverse effects to the lungs. Furthermore, in some tobacco products, the burning of the substance may cause changes and degradation of the compounds forming unknown products.

The tobacco industry has claimed that the additives they use in tobacco products are safe and stated that they are Generally Recognized as Safe (GRAS) by the US FDA (Food and Drug Administration) and listed in the FEMA (Flavour and Extract Manufacturer Association) GRAS flavouring substances.

A close look at the definition and use of the terminology GRAS for additives, both under the FDA and FEMA points of view, shows that:

1- GRAS is an acronym for the phrase Generally Recognized As Safe. Under sections 201(s) and 409 of the U.S. Federal Food, Drug, and Cosmetic Act (the Act), any substance that is intentionally added to food is a food additive, that is subject to premarket review and approval by FDA, unless the substance is generally recognized, among qualified experts, as having been adequately shown to be safe under the conditions of its intended use, or unless the use of the substance is otherwise excluded from the definition of a food additive.

2- The specific data and information that demonstrate safety depend on the characteristics of the substance, the estimated dietary intake under the intended conditions of use, and the population that will consume the substance.

3- Under section 201(s) of the Act, it is clearly stated that it is the use of a substance, rather than the substance itself, that is eligible for the GRAS exemption (62 Fed. Reg. 18939; April 17, 1997).

4- FDA has defined "safe" (21 CFR 170.3(i)) as a reasonable certainty in the minds of competent scientists that the substance is not harmful under its intended conditions of use.

5- The FEMA Expert Panel only evaluates substances for GRAS status that are used to formulate flavours to be added to human foods.

The Expert Panel does not evaluate food ingredients with functions other than flavouring nor does it evaluate flavourings for use in products other than human food. For example, the FEMA Expert Panel is explicit in its statement that its findings are NOT relevant to tobacco products:

> *"The FEMA Expert Panel only evaluates substances for GRAS status that are used to formulate flavours to be added to human foods. The Expert Panel does not evaluate food ingredients with functions other than flavouring nor does it evaluate flavourings for use in products other than human food. For example,* ***the Expert Panel does not evaluate flavour ingredients for use in tobacco products, e-cigarettes, or other products that involve routes of exposure other than ingestion."*** *(emphasis added)*
> (FEMA, 2014; available at http://www.femaflavour.org/gras)

From the above it is clear that **the concept of GRAS is only applicable to food additives**, which are substances intentionally added to food to achieve a certain purpose. For a food additive to be GRAS, there must be evidence that the substance is safe under the conditions of its intended use.

As the intended use of flavourings in tobacco products involves a route of exposure that has not been previously evaluated by the Expert Panels that evaluate substances for GRAS status, there is no evidence of safety under these conditions of use.

As a consequence, flavouring additives used in tobacco products **cannot be considered GRAS for this intended use**.

Moreover, the Codex Alimentarius itself states that food does not include tobacco products. They state explicitly:

> *"Food means any substance, whether processed, semi-processed or raw, which is intended for human consumption, and includes drink, chewing gum and any substance which has been used in the manufacture, preparation or treatment of "food" but* ***does not include cosmetics or tobacco or substances used only as drugs."*** *(emphasis added)(FAO Codex Alimentarius Committee;* http://www.fao.org/docrep/005/y2200e/y2200e07.htm)

Based on the above considerations, the WG concludes that the consistent claims by Abifumo and the tobacco industry more generally that GRAS status has relevance for tobacco products is not valid.

b. Toxicity

Given the current toxicity tests and test designs, it is not yet possible to determine whether or not addition of specific ingredients (tobacco additives) to tobacco products adds to tobacco mainstream smoke's inherent toxicity. This is because tobacco itself is already quite toxic, and any added toxicity is difficult to detect within the current test designs used by tobacco industry, i.e. combinations of *in vitro* testing and animal testing.

The tobacco industry in general tends to test mixtures of ingredients (Coggins, Edmiston, et al., 2011; Coggins, Fisher, Smith, & Oldham, 2011; Coggins, Frost-Pineda, Smith, & Oldham, 2011; Coggins, Jerome, Edmiston, & Oldham, 2011; Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA), 2004; Roemer, Tewes, Meisgen, Veltel, & Carmines, 2002), or individual ingredients (Coggins, Liu, Merski, Werley, & Oldham, 2011; Coggins, Merski, & Oldham, 2011; Coggins, Sena, Langston, & Oldham, 2011; Coggins, Sena, & Oldham, 2011; Coggins, Wagner, Werley, & Oldham, 2011; Gairola, Drawdy, Block, & Daugherty, 2001; Life Sciences Research Office (LSRO), 2007; March et al., 2006; National Research Council, 2007; Rustemeier, Stabbert, Haussmann, Roemer, & Carmines, 2002) by a comparative testing approach (cigarette with vs cigarette without the additive) using toxicity tests for *in vitro* and *in vivo* endpoints. Results of these studies show that some smoke components are significantly increased in test versus reference cigarettes, e.g., the carcinogenic formaldehyde (Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA), 2004). However, common findings in all studies are that the comparative testing approach does not provide significant results on measured toxicity endpoints, even though harmful smoke components may be increased. In other words, there is no increase in mutagenicity, chromosomal damage, or respiratory tract or other organ toxicity in cigarettes to which the additive (mixtures) are added compared to reference cigarettes that only differ in their lack of the additive (mixture) (Cooperation Centre for Scientific Research Relative to Tobacco (CORESTA), 2004; Roemer et al., 2002; Rustemeier et al., 2002).

In the early to mid 2000s, a number of studies sponsored by the tobacco industry addressing the effect of mixtures of commonly used additives on the smoke chemistry and toxicity were published in toxicological journals (Carmines, 2002). In a preface to a special issue of *Food and Chemical Toxicology* on the effects of tobacco ingredients on smoke chemistry and toxicity, (Baker, 2004) summarized the conclusions of these industry studies by stating that "…*commonly used tobacco ingredients do not change toxicity of smoke as measured in specified assays*" and also that *"..the ingredients have no effect on the levels of most smoke constituents that may be relevant to smoking-related diseases*".

The conclusions of industry-sponsored studies suggesting that additives do not add to smoke toxicity, however, were questioned by independent researchers (e.g., Schwenk, Thielmann, Potschke-Langer, & Wiebel, 2010; Wertz, Kyriss, Paranjape, & Glantz, 2011). Wertz et al. (2011) pointed out that these studies by tobacco industry researchers in fact showed an increase in total particulate matter (TPM) concentration and toxicity in the smoke of cigarettes containing additives compared to that of reference cigarettes devoid of additives. According to Wertz et al. (2011) the conclusion that there was no evidence of toxicity attributable to tobacco additives was reached only after expressing the data adjusted by TPM concentration. A study by Rustemeier et al. (2002) for instance revealed that levels of TPM per cigarette in the mainstream smoke increased in three groups of additive/ingredient mixtures (333 commonly-used additives were assigned to three groups containing different mixtures of casing materials and flavouring ingredients). Data by Rustemeier et al. (2002) also indicated that levels of a number of toxicants including formaldehyde, benzo[*a*]pyrene, cadmium, lead and others, also increased in the smoke of additive-containing cigarettes. In another study by the same group, Vanscheeuwijck et al. (2002) compared the mainstream smoke from control cigarettes without additives with that of a cigarettes containing mixture of additives in a rat subchronic inhalation (nose-only, 6h/d, 7d/week for 90 days) toxicity study. The authors reported that findings in the respiratory tract of the rats exposed to reference cigarettes did not differ from those in rats exposed to smoke from additive-containing cigarettes, albeit both groups were severely affected compared to a control sham-group (not exposed to cigarette smoke). As commented by Wertz et al. (2011), in this study TPM levels in the inhaled smoke were kept constant at 150µg/L in all groups.

Considering the toxicity testing strategies using the comparative testing approach, all proposed assays are validated toxicity tests used for safety testing of substances in chemical and pharmaceutical industries for which guidelines are provided by the Organisation for Economic Co-operation and Development (OECD) (Organisation for Economic Co-operation and Development (OECD), 2013). However, it is argued that any current battery of toxicity tests cannot adequately assess the contribution of additives and their pyrolysis product(s) to the overall toxicity (Committee on Toxicity, Committee on Mutagenicity, & Committee on Carcinogenicity of Chemical in Food, 2009). Furthermore, some argue that toxicity tests may not yet be suitable to assess toxicity of tobacco product emissions at all, given the sometimes negative or weak results of tobacco smoke in carcinogenicity tests, regardless of the causal relation between tobacco smoke and cancer (Committee on Toxicity et al., 2009).

Overall, results from this set of industry-sponsored studies indicated that addition of tobacco-additive changes mainstream smoke regarding TPM and some other toxicants. It is debatable whether or not TPM levels should be adjusted to test the influence of additives on tobacco smoke inhalation toxicity because tar content levels are fixed in commercial cigarettes. At any rate, a sub-chronic inhalation toxicity study is insufficient to make inferences regarding influence of tobacco additives on long-term carcinogenic effects of tobacco smoke.

Evaluation of data from toxicity studies provided by tobacco industry (Abifumo reports and literature search) and all the information obtained in the literature led the WG to conclude that currently available evidence is insufficient to support the conclusion that tobacco additives have no impact on tobacco smoke inhalation toxicity.

In the food and chemical industry, individual substances to be used in products must be fully characterized in short- and long-term bioassays, regarding their toxicity including carcinogenicity, mutagenicity and reprotoxicity. A full risk assessment of individual substances determines whether regulatory agencies approve or reject their use. These regulations have not yet been applied to tobacco products.

In 2010, the German Cancer Research Center (Deutsches Krebsforschungszentrum or DKFZ) proposed a tiered approach for the toxicity testing of tobacco additives based on the concept that there is no reason to exempt tobacco products from additive toxicity testing for regulatory purposes (Deutsches Krebsforshungzentrum (DKFZ), 2010). Additives deliberately added for design purposes should be safe, according to current toxicity standards, in unburnt and burnt form, at least in the amount present after burning using realistic standardized methods.

Here, the precautionary principle is employed whereby a tiered approach is used for the toxicological evaluation of additives. In the first-tier "*toxicological evaluation of additives in their unburned form*", all available information on the additive in unburnt form is collected and evaluated. This includes for example JECFA and FEMA data. When the additive in unburned form shows any signs of toxicity, the additive is rejected. In the second-tier "*toxicological evaluation of pyrolysis products*", sufficient information available on pyrolysis products of additives (Paschke, Scherer, & Heller, 2002; Rodgman & Perfetti, 2012) can be collected and evaluated, and when sufficient, result in a possible decision. For instance, many **toxic** (including carcinogenic) smoke compounds are generated from sugars, such as formaldehyde, a class 1A carcinogen. When pyrolysis data is not available, in the third-tier "*pyrolysis of additives and toxicological evaluation of the products*", new data should be generated. For this, methods that use realistic, standardized conditions should be used. The fourth and last tier describes "*toxicological testing of additives or their pyrolysis products*", according to regulations that also apply for food and chemical industry (Deutsches Krebsforshungzentrum (DKFZ), 2010).

The WG supports the German Cancer Research Center's tiered approach for the testing of the toxicity of tobacco additives and recommends that it be the foundation of an approach to testing for tobacco additives in Brazil.

c. Addictiveness

Addiction is what leads to persistent use of a tobacco product and difficulty quitting, thereby having a negative impact on public heath as a result of continued exposure to toxicants in the product. The addictiveness of a product refers to the pharmacological potential of a substance to cause addiction (or dependence; Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), 2010). The addictiveness of a substance is not only dependent on its central nervous system effects, but also the dose, speed of delivery or absorption, metabolism, and the formulation of the product. While nicotine is the primary addicting substance in tobacco, Technical Report 008/2013—GGTAB/ANVISA describes additives as potentially contributing to addictiveness of a product by: a) serving as a reinforcer itself; 2) increasing the bioavailabilty of nicotine (e.g., increasing levels of free nicotine) 3) increasing exposure to nicotine (e.g., enhancing bronchodilation); 4) decreasing the clearance of nicotine (e.g., inhibition of CYP2A6); or 5) potentiating nicotine's reinforcing properties (e.g., inhibition of MAO).

For instance, sugars generate acetaldehyde, which has addictive properties and acts synergistically with nicotine in rodents (Bates, Jarvis, & Connolly, 1999; Belluzzi, Wang, & Leslie, 2005; Gray, 2000; Henningfield et al., 2004). It has been speculated that acetaldehyde reacts with biogenic amines to condensation products that inhibit monoamine oxidase, an enzyme that degrades biogenic amines, like dopamine and noradrenalin (Belluzzi et al., 2005; Jamal et al., 2003; Villegier, Blanc, Glowinski, & Tassin, 2003). The brain levels of these aminergic neurotransmitters, known to be involved in drug addiction (Koob, 1992), increase as a result of the inhibition of monoamine oxidase.

The WG agrees that these are potential mechanisms by which additives can enhance the addictiveness of a tobacco product. Furthermore, the WG believes that the addictiveness of tobacco additives have not been sufficiently tested by the tobacco companies. Various validated methods to assess addictiveness (also known as *abuse liability)* of pharmacological drugs, potential drugs of abuse, and nicotine/tobacco have been described (e.g., Balster & Bigelow, 2003; Carter & Griffiths, 2009; Expert Panel, 2003; Food and Drug Administration, 2010). In a meeting of scientific experts that was convened to discuss methods for assessing addictiveness (also known as *abuse liability assessment (ALA))* of tobacco products, the following conclusions were reached (Henningfield, Hatsukami, Zeller, & Peters, 2011):

- *Laboratory based abuse liability assessment (ALA) using human and non-clinical testing protocols has been shown to have good predictive ability for real world abuse of drugs acting on the central nervous system as evidenced by the utility of such methods in guiding the regulatory control of various opioids, sedatives, and stimulants, in accordance with their potential for abuse and dependence (cf. Expert Panel, 2003; Food and Drug Administration, 2010; Johanson et al., 2009).*

- *Abuse liability of a product is most accurately achieved by using multiple tests for its evaluation. Tests may include analysis of constituents and product design factors associated with potential for addiction, animal studies, human laboratory and clinical trials, and surveillance (Carter et al., 2009).*

- *Tobacco products are complex formulations that make ALA a multifaceted undertaking that may involve assessment of several pharmacologically active constituents [and emissions] (e.g., nicotine, acetaldehyde, anabasine, and nornicotine) in some products as well as contents that could influence nicotine delivery speed and efficiency (e.g., buffering agents) and design features that influence nicotine release and the formation of unprotonated nicotine (e.g., tobacco cutting size and ventilated filters) (Carter et al., 2009).*

- *Nicotine is considered to be the primary addictive agent in tobacco and can exist in different forms that may vary in pharmacological activity. Specifically, unprotonated nicotine (also known as "free nicotine"), unlike the protonated form, is more likely to migrate into the gas phase and is highly lipophilic; it also more readily moves across the mucosal membranes and reaches nicotinic receptors faster than protonated nicotine (Hoffman & Hoffman, 2010; Wayne, Connolly, & Henningfield, 2006). Unprotonated nicotine levels may be altered by pH and by design features such as filter ventilation (Ashley, Pankow, Tavakoli, & Watson, 2009; Watson, Trommel, & Ashley, 2004).*

- *It was suggested that non-nicotine constituents including, but not limited to, acetaldehyde, MAO inhibitors….(Benowitz, Hukkanen, & Jacob III, 2006; Hoffman & Hoffman, 2010), and menthol might also contribute to AL [abuse liability] through various actions such as stimulation of trigeminal neurons in addition to or instead of central nervous system effects (Megerdichian, Rees, Wayne, & Connolly, 2007; Wayne & Carpenter, 2010; Wayne, Connolly, & Henningfield, 2004).*

- *Abuse liability might also be influenced by ingredients and design features that facilitate the inhalation and absorption of nicotine into the lung by reducing harshness of the smoke, such as by filter ventilation and smoke "smoothing" and throat "soothing" smoke constituents such as menthol (Ashley et al., 2009; Okuyemi, Lawrence, Hammons, & Alexander, 2010; Wayne & Carpenter, 2010).*

On the other hand, SCENIHR has documented concerns with the validity of current testing, owing to limitations on human testing and the lack of predictive validity of animal studies:

- *Many different methods are used in humans, but there is a lack of consistency between them. Human studies have limitations in design (e.g. the use of conditioned cues, and the need to work with smokers). Furthermore, ethical issues may arise when testing substances in humans. There is currently no animal model to assess the addictive potency of the final tobacco product; however, pure nicotine has been studied extensively. The experimental animal models are mainly based on self-administration in rodents, usually rats. The evaluation of addictiveness is based on the reinforcing properties of the drug. However, there is no consensus on the predictive validity for the addictiveness of tobacco products in humans.*

The WG believes that existing methods for evaluating addictiveness leads to a more optimistic conclusion than that of SCENIHR. As noted above, human studies have demonstrated their validity in predicting the abuse liability of a substance (Carter & Griffiths, 2009; Carter et al., 2009; Expert Panel, 2003; Henningfield et al., 2011), even when conducted in a substance-using population, as described in the U.S. FDA draft guidelines for the assessment of abuse potential of drugs (2010). These ALA methods have been used by the U.S. FDA and other drug regulatory agencies worldwide for decades to assess the risk for addiction posed by a wide variety of drugs. For example, studies using ALA methods provided key data to the U.S. Surgeon General in the 1980s and later by the FDA in their determinations that nicotine in cigarettes met the objective criteria as an addictive drug. The various ALA methods to test the addictiveness of tobacco products in humans are described in several review articles (e.g., Carter et al., 2009; Hatsukami et al., 2009), and studies are ongoing to determine the validity of these models in testing tobacco products.

With regards to the testing of the final tobacco product using animal models, more recent studies have tested aqueous extracts of smokeless tobacco products (Harris, Stepanov, Pentel, & Lesage, 2012) and cigarette smoke (Brennan, Putt, Roper, Waterhouse, & Truman, 2013; Costello et al., 2014; Harris, Mattson, Lesage, Keyler, & Pentel, 2010) using intracranial self-stimulation or self-administration procedures. Understandably, the route of administration is not similar to humans, yet these results can be used to support findings observed in humans. That is, animal studies alone would not be used to support the addictiveness of a tobacco product. As described in the Carter et al. article (2009), it is the combination of studies employing ALA methods that should be used to determine the abuse liability of a tobacco product (or its constituents).

For these reasons, the WG concludes that there currently exist methods that could be reasonably used to assess the addictiveness of additives in tobacco products. It is the convergence of studies employing different ALA methods that would lead to an evidence-based conclusion about an additive's addictiveness.

To date, no additive and its combustion products, either singly or in mixtures, has undergone comprehensive testing of its addictiveness using the various methods described above. Therefore, at present, there is **no convincing evidence that was provided to the WG that would suggest that additives are not addictive or do not contribute to the addictiveness of tobacco products**.

d. Attractiveness

Attractiveness of a product refers to any factors that can enhance its appeal or palatability to consumers, thereby stimulating its use (the Framework Convention on Tobacco Control Partial Guidelines for the Implementation of Articles 9 and 10 and Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), 2010). SCENIHR (2010) reports that the factors that can influence attractiveness are both extrinsic to the product (e.g. marketing, packaging, pricing), and intrinsic to the product (e.g. taste, smell, sensory attributes, and pharmacological effects). Additives can increase attractiveness by improving the smell, taste and aroma, reducing harshness and irritation, and enhancing smoothness or the sensory attributes of tobacco smoke. In these ways, additives can enhance the palatability of the product and also help promote the misimpression that such products are less harmful. As a consequence, additives can play a significant role in the initiation and sustained use of tobacco products.

The importance of additives in affecting the attractiveness of a tobacco product, particularly in the beginning smoker, is described in an article written by Talhout et al. (working paper 2014):

> "*It is well-known that in addition to the addictive effects of nicotine, sensory product characteristics such as taste, aroma, and respiratory tract sensations (mouth feel, impact) play a major role in smoking satisfaction, product acceptance, and the desire to smoke (Levin et al., 1993; Rose, 2006). ….Regarding taste and aroma, cigarette smokers identify flavour as an important factor in the pleasure derived from smoking and for their choice of cigarette brand (DiFranza, Eddy, Brown, Ryan, & Bogojavlensky, 1994; Leatherdale, Ahmed, Barisic, Murnaghan, & Manske, 2009; Levin, Behm, & Rose, 1990). Dutch survey data also indicate that taste and smell are important determinants of brand preference among adolescent smokers (Talhout, Sleijffers, Van Amsterdam, & Opperhuizen, 2009). For instance, the sweetness of cigarette smoke appeared closely related to satisfaction and pleasantness (Jaffe & Glaros, 1986). Apart from a good taste and aroma, other important sensory factors include satisfaction, and low irritation to mouth, throat and chest, particularly for novice smokers (Jaffe & Glaros, 1986; Kochhar & Warburton, 1990). Mildness, a combination of improved aftertaste, less bitterness, improved mouth feeling and reduced irritation, is reported to be appreciated, especially by younger and beginner smokers with their undeveloped tastes and a low tolerance for irritation from tobacco smoke (Carpenter, Wayne, & Connolly, 2007; Ling & Glantz, 2002)." (Talhout et al., working paper 2014)*

One example of additives that have effects on sensory product characteristics is sugars. Sugars generate acids that neutralize the harsh taste and throat impact of tobacco smoke. These acids decrease smoke pH, which in turn decreases the free-base nicotine level in mainstream smoke. As a result, the impact, "nicotine strength", harshness and irritation of the smoke will decrease as well (Creighton & Hirji, 1988; Elson, Betts, & Passey, 1972; Leffingwell, 1999; Rodgman, 2002; Shelar, Bernasek, & Furin, 1992). Throat impact and harshness decrease as the sugar level increases, until a plateau value of around 10% (Shelar et al., 1992). Consumer acceptance of tobacco smoke is proportional to the sugar level in tobacco (Rodgman, 2002; Shelar et al., 1992).

Furthermore, combustion/pyrolysis of sugars generates caramel flavours in tobacco smoke, which give it a sweet taste that masks the aversive bitter taste of cigarette smoke. As a result, people (in particular youth) may find the product more palatable and this may make it easier for them to take up smoking and to progress to regular use.

It is also clear from the tobacco industry documents that a primary objective of some additives is to increase the attractiveness of their products in order to increase consumer demand. It follows directly, therefore, that if additives are banned this has the potential to decrease consumer demand, and thus the potential to improve public health. The WHO Partial Guidelines for the Implementation of FCTC Articles 9 and 10 states the basic principle in this way:

> *"Tobacco products are commonly made to be attractive in order to encourage their use. From the perspective of public health, there is no justification for permitting the use of ingredients, such as flavouring agents, which help make tobacco products attractive."*

The Partial Guidelines further state:

> *"The harsh and irritating character of tobacco smoke provides a significant barrier to experimentation and initial use. Tobacco industry documents have shown that significant effort has been put into mitigating these unfavourable characteristics."*

As a consequence of the important role of product attractiveness on uptake and continued use of a product, the Partial Guidelines for the Implementation of FCTC Articles 9 and 10 included the recommendations that Parties should:

> 1) regulate, by prohibiting or restricting ingredients that may be used to increase the palatability of the product (as defined those ingredients that as mitigate harshness or irritation of tobacco smoke); 2) prohibit or restrict ingredients that have colouring properties in tobacco products (except the use of colouring agents for tax-related markings or for health warnings); 3) prohibit ingredients in tobacco products that may create the impression that they have a health benefit; and 4) prohibit ingredients associated with energy and vitality.

With regards to testing the impact of additives on the attractiveness of a tobacco product, the WG believes it is insufficient to rely on cross-country comparisons, because there are many confounding differences between countries, including type of tobacco used, the configuration of additives that are included in the tobacco products, and differences across countries in the historical development of the tobacco market. Based upon the deliberations of a meeting of scientific experts described above in the Addictiveness section, Henningfield et al. (2011) concluded that there are methods to test attractiveness of products that do not rely on cross-country comparisons:

"Product appeal can be scientifically evaluated according to standardized protocols in laboratory and non-laboratory settings through sensory and subjective assessments of consumer risk perceptions, responses to products, and product acceptability, and such methods are routinely used in product development for new foods, beverages, detergents, and other consumer goods, as well as for new tobacco products (Rees et al., 2009; Slovic, 2001)."

The WG concludes that the documents that were reviewed do not provide sufficient data, based on adequate and methodologically sound testing methods, to demonstrate that additives do not increase the attractiveness of tobacco products.

In fact, some of the most well-designed studies appear in the tobacco industry documents. Moreover, these industry studies involve human subjects and thus are immune to the criticisms that non-human studies are not relevant to human experience. These industry studies of the impact of various additives, individually and in combination, demonstrate that additives can indeed increase attractiveness by improving taste, imparting flavours, reducing harshness, increasing smoothness, and increasing other desirable characteristics. The WG is particularly concerned about the influence of additives on the uptake of tobacco use and progression to regular use among youth and other special groups. The WG is also concerned about the impact of flavours on reducing the likelihood of quitting, effects that have been noted by the US FDA (Food and Drug Administration, 2013; Tobacco Products Scientific Advisory Committee, 2011).

With respect to the distinction that is made between "characterizing" and "non-characterizing" flavours, the WG believes that this distinction is a misleading one with respect to public health. For example, although some brands have menthol as their "characterizing flavour", menthol or constituents that together lead to menthol-like effects are added to many other brands because of their impact on reducing harshness and irritation from smoking, regardless of whether the smoker can perceive their flavour.

However, there is one aspect of "characterizing flavours" that is of additional concern to the WG: products with a "characterizing flavour" provide an opportunity for the industry to increase their attractiveness using methods that go beyond the sensory and perceptual attributes of the product, for example, marketing efforts such as packaging, messages, and images that are associated with the flavour (Henningfield et al., 2011), especially those that are targeted to sub-populations such as youth, minorities, and women (Tobacco Products Scientific Advisory Committee, 2011). It is also important to note that it is possible to create the perception of a flavour (e.g., menthol) through a combination of different additives or constituents. **The WG considers that this possibility justifies the banning of all additives, rather than merely "characterizing flavours."**

C. Comments on Abifumo's Submission: "Comments on Tobacco Ingredients (or Additives) Usage in Brazil", July 7, 2014

The arguments and most of documents presented in the submission of July 7, 2014 were already provided by the Anvisa's Presidencia and analyzed by the WG. The documents bring no new arguments to contribute to the discussion. Most of the issues that were raised in this document are addressed in the sections above. However, we would like to make several additional points in response to the Abifumo Submission:

1. An assumption that is apparent throughout Abifumo's submissions is that the burden of proof is with Anvisa to demonstrate that the use of additives is harmful to health and that they enhance attractiveness. However, it is common practice that the producer of a consumer product is responsible for demonstrating its safety. Thus, the burden of proof is with the tobacco companies to demonstrate, through comprehensive scientific evidence, that the use of additives is safe (not harmful to health) and they DO NOT enhance addictiveness or attractiveness of the product. This position on burden of proof is clearly stated by Anvisa in its technical reports, and it is one that the WG supports because, as just explained, it is consistent with the common practice in consumer safety.

2. Another assumption that is apparent in the submissions is that the critical test of the harmfulness to health of an additive, according to Abifumo, is if that additive makes a tobacco product **more harmful to health that it already is.** However, the relevant test for whether an additive is (potentially) harmful to health is NOT whether it makes a tobacco product more harmful. The proper test, in our view, is that which is outlined in the German Cancer Research Center report on tobacco additives: that the additive being tested should be tested by itself. This is in line with practices in the food and chemical industry: individual substances to be used in products must be fully characterized in short- and long-term bioassays. Also, the evaluation of toxicity should be performed in the manner in which the user of tobacco products is exposed: specifically, in the case of cigarettes the additive and the products produced by pyrolysis of that additive should be tested under conditions relevant to exposure through inhalation because that is the circumstance under which smokers are exposed to that additive. If the combustion products of the additive contain toxic compounds, then it can be concluded that the additive is harmful to health. Although the WG believes that mixtures of additives should also be tested because of the possibility of synergistic effects, the reason the WG agrees that testing single additives should be considered as one of the primary methods of assessments is because demonstrating that adding additive(s) to an already extremely toxic tobacco product is likely to be very difficult.

3. Reference to GRAS is not sufficient to demonstrate the safety of an additive. GRAS is used with reference to the safety of food additives as tested under the conditions of its intended use; again, it is not relevant to additives that are burned or used in the context of other exposure routes or in the presence of toxic chemicals. In the case of cigarettes, the standard for testing should be the impact of the product when it is burned and inhaled in the lungs. This is a principle that has been stated explicitly by expert authorities such as the FEMA Expert Group, the US FDA, and the FAO/WHO Expert Committee on Food Additives. Thus, if an additive is designated as GRAS when used in food, that designation cannot be used to claim that the additive has the same status when used as a tobacco additive.

4. The assessment of the impact of a tobacco additive on public heath does not solely rest on its toxicity, but also, in line with guidelines of article 9 and 10, on addictiveness and attractiveness as described above. The WG believes that, because of this, Anvisa is justified in calling upon the tobacco industry to not only demonstrate that an additive is not harmful, but also that it does not contribute to the addictiveness of the product, and does not increase the attractiveness of the product to consumers (including selected subgroups of the consumer population or potential consumers, especially youth); and that any additive must pass all three criteria as evaluated both by itself or in combination with other additives and constituents of the tobacco product.

5. Abifumo stated that “nicotine is not added during the manufacturing process, nor does the manufacturing process increase the amount of nicotine found naturally in the tobacco used in the products.” However, nicotine is not the sole component responsible for tobacco addiction. It is well known that the addictiveness of a tobacco product can be enhanced with the use of additives that serve as a reinforcer, that enhances the bioavailability of nicotine or increases exposure to nicotine. It is the task of the tobacco companies to show that these additives do not serve these functions.

6. The proof that additives do not enhance the harm or the uptake of a product cannot rest only on data from cross-country comparisons. There are other differences between countries that may influence preferences for tobacco products besides the presence or absence of additives in these products, such as tobacco type used (there are also large differences in taste in natural tobacco to such extent that additives need not be used in some types of tobacco) and cultural practices. Other more valid methods for evaluation of the toxicity, addictiveness, and attractiveness of products are described above.

7. Abifumo’s documents indicate that no scientific criteria have been developed to measure the “attractiveness” of tobacco products. However, tobacco industry documents themselves are very clear in documenting the importance that the industry places on identifying additives that would increase the attractiveness of cigarettes. Some of these additives have been studied with respect to their impact to reduce harshness; others have been identified because they add flavour to cigarettes, thereby making them more attractive. The measures of attractiveness that are used in such industry studies are reasonable: asking for self-reports of whether smokers like the taste, whether the cigarette is harsh or smooth (and gradations in between), and whether they would like to smoke that type of cigarette again.

8. The Abifumo documents state that: “Most of the substances on the RDC 14 list have been found in tobacco. It is very difficult and often impossible through technical analysis to establish whether the presence of a substance in a finished tobacco product is due to its occurring naturally in tobacco or due to its being added. Thus, as a practical matter, it would be exceedingly difficult for Anvisa, tobacco manufacturers, retailers or any other interested parties either to detect the presence or to confirm the absence of the wide range of substances banned as cigarette additives, with regard to any particular sample of tobacco or cigarettes.”

With respect to what kinds of policies and regulations would benefit public health, the WG sees no public health distinction whether a substance is added to a tobacco product and whether that substance is “naturally occurring” in tobacco. If it is toxic or is addictive or leads to greater attractiveness of the product, from a public health standard, that substance should be considered to be banned.

D. Conclusions

From the review of the material relevant to RDC 014/2012, the WG reaches the following conclusions:

1. The WG concludes and reaffirms prior conclusions of others that the safety of additives for use in tobacco products cannot be inferred from safety assessments of their use in human food. It is the way in which the substance is used, rather than the substance itself, that makes it possible to assess its eligibility for the designation of GRAS. Flavouring additives used in tobacco products cannot be considered GRAS because they are used differently (e.g., many additives in cigarettes are subjected to burning and inhaled rather than eaten).

2. The WG concludes that a proper testing procedure for assessing the toxicity of a tobacco additive is the method described by the German Cancer Research Center: to test that additive singly, outside of the product, under the conditions of its use. Thus, for example, each additive used in cigarettes should be subjected to pyrolysis testing, and **tests relevant to exposure through inhalation must be performed for the additive and for the products produced by pyrolysis of that additive**. The studies conducted by the tobacco industry fail to support their conclusions about the lack of toxicity of tobacco additives.
3. Methods for testing the addictiveness of substances have not been adequately and systematically used by the tobacco companies to test the addictiveness of tobacco additives. Moreover, according to groups such as SCENIHR, such methods may still require further testing and validation. Therefore the WG did not see any evidence demonstrating that additives do not contribute to the addictiveness of tobacco products.
4. The WG concludes from its review of the materials that attractiveness or appeal should be at least as important as toxicity or addictiveness as a criterion for assessing the impact of additives on health.
5. Tobacco industry documents provide a rich compilation of studies demonstrating the powerful impact of additives on increasing the attractiveness and appeal of tobacco products. Many of the studies use experimental designs to evaluate the impact of many additives, both singly and in combination with others, and have the advantage of high relevance and validity because they involved human participants. These studies show that additives are used to improve taste, reduce harshness or irritation and to enhance the sensory experience of tobacco products to increase their appeal. The WG concludes that there is ample evidence to support a ban on tobacco additives because of their demonstrated effects of increasing the attractiveness of tobacco products.
6. The WG concludes that the submission by Abifumo of July 2014 repeats prior arguments that, for the most part, had already been effectively addressed by Anvisa. The WG further concludes that in the submissions made by Abifumo, there was insufficient evidence presented on the 121 additives regarding the three criteria used to determine impact on public health: toxicity, addictiveness, and attractiveness.
7. The WG concludes that RDC 14/2012 when fully implemented has the potential for significant reductions in tobacco consumption and therefore significant reductions in tobacco-related diseases and death.
8. The WG recommends that the RDC 14/2012 be amended so that sugars are no longer excluded from the additive ban. Sufficient scientific evidence exists for the impact of sugars on increasing the attractiveness of tobacco products, which is described by Abifumo itself (e.g., improving the taste) and consistent with many tobacco industry documents (e.g., as described in Roemer et al., 2012; Sokol, Kennedy, & Connolly, 2014). Sugars, when burned, produce aldehydes (Talhout, Opperhuizen, & van Amsterdam, 2006), some of which (e.g., formaldehyde) have been identified by IARC as Class 1A Carcinogens. Thus, sugars should be banned under the single-component toxicity test. From a public health standpoint, there is insufficient cause to exclude sugars from the additive ban.
9. The WG recommends that an effective monitoring and enforcement structure be set up for ensuring that the provisions established by RDC 14/2012 are followed.
10. The WG recommends that a comprehensive program of evaluation be established for assessing and understanding the impact of RDC 14/2012 on tobacco use, perceptions of tobacco products, and other key evaluation criteria. Such a program would be valuable for providing feedback for Anvisa as well as for other countries who may be interested in following Brazil's regulatory action on additives.

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