ADDITIVES, CIGARETTE DESIGN and TOBACCO PRODUCT REGULATION

A REPORT TO:

WORLD HEALTH ORGANIZATION
TOBACCO FREE INITIATIVE
TOBACCO PRODUCT REGULATION GROUP

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FOREWARD

This paper is written with the perspective of over 15 years experience and involvement in tobacco science and chemistry. As the Vice President of Research, Development and Environmental Affairs for Brown & Williamson Tobacco Corporation, I became intimately aware of the philosophy of additive(s) use, and of how the industry's lawyers buffered the meaningful disclosure of these additives.

Most recently, I have served as the expert in the Dutch litigation concerning the Netherlands' transposition of EU Directive 2001/37/EC into Dutch law ("Dutch Decree"). The Dutch Decree requires manufacturers and importers of tobacco products to disclose all additives by quantity, type and by brand name. Unsurprisingly, the tobacco industry initiated litigation to prevent the enactment of this law. The Dutch Decree has been tested in the Dutch Courts with a preliminary opinion rendered, and the legal action is pending final resolution. My knowledge of both intentional and unintentional additives (contaminants) was used to respond to the industry's argument that additive disclosure is not only scientifically superfluous, but also violates the industry's trade secrets.

It is my opinion that an adequate regulatory framework for additives requires the industry to disclose both intentional and *unintentional* additives or concomitants. The Dutch Decree as well as the WHO FCTC address only the former concern. However, as I discuss in Part III of this report, unintentional additives also pose risks to public health. For example, packaging inks, microflora, and solid contaminants such as styrofoam, are among the unintentional ingredients that are inhaled by the smoker. The effective regulation of tobacco products should either prohibit or restrict unintentional additives that pose risks to public health.

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INTRODUCTION

Smallpox killed approximately 300 million people in the 20th century, three times the number of all war related deaths. Today, the scourge of smallpox has been eradicated. Smallpox has no animal reservoir and its infection is solely limited to humans. The congruency between smallpox and tobacco induced diseases is not trivial, and as smallpox did not discriminate between kings or serfs, neither does tobacco. The addicted adult user, the adolescent novice, and the innocent bystander are all vulnerable to the harms of tobacco.

In 2005, the World Health Organization (WHO) decided to take action to protect the public from the harms of tobacco by devising a regulatory model for tobacco, the Framework Convention for Tobacco Control (FCTC). The FCTC sets in motion a series of actions directed at *"denormalizing"* tobacco, such as restriction on advertising and sponsorships, changes in packaging, and the proliferation of smoke free environments. The Convention, through the Conference of Parties (COP), Article 9, identified the need "for testing, measuring and regulating the contents and emissions of tobacco." The need is critical indeed.

Tobacco products are not “natural” products that contain harmless ingredients. Rather, a typical cigarette can contain numerous intentional additives. However, virtually nothing is known about these ingredients. Even worse, nothing is known about the *un*intentional additives that are the by-products of the growing, handling and manufacture of tobacco products. These unintentional additives or contaminants include pesticides, herbicides and ink from the packaging materials. We are in the dark about how these unintentional additives are affected when burned in conjunction with nicotine and when combusted with other intentional additives.

The objective of this manuscript is to produce a scientifically relevant instrument that will enhance the understanding of the role of both intentional and unintentional additives in the

morbidity and mortality of tobacco products. Throughout this manuscript the terms "additive," "ingredient," and "flavoring" will be used synonymously. Although I limit discussion to additives in *conventional cigarettes*, the use of additives in non-conventional cigarettes and in other tobacco products is also pervasive. These areas are in need of attention, and future research on tobacco additives should include research into these devices.

This manuscript begins with a discussion about cigarette design. In order to understand how additives function, one must first understand the design features of cigarettes. As we will see, some of these design features affect the delivery of additives. For example, the introduction of reconstituted tobacco or RECON, is the primary means by which ammonia chemistry and other chemicals are introduced into a cigarette. RECON can be considered a "chemical delivery" system.

After outlining cigarette design, I will then address the topic of intentional additives. The industry argues that since all intentional additives are GRAS ("generally recognized as safe") approved, then there is no need for disclosure of these additives. I explain why this argument is bogus. I also discuss some of the chemical properties of several of the additives that are typically used in US blended cigarettes (sugars, glycerol, etc.). I then turn my discussion to unintentional additives. There are a variety of hazardous chemicals resulting not only from the soil in which tobacco is harvested, but also from the packaging in which cigarettes are housed. These chemical entities are typically ignored. However, any policy concerned with mitigating the harm caused by tobacco products needs to be mindful of the harm posed by unintentional additives.

I.CIGARETTE DESIGN

While there are many different kinds of tobacco products (e.g., cigarettes, cigars, cigarillos, bidis, kreteks, pipe tobaccos, and smokeless products), the most common form of tobacco is the manufactured cigarette. A cigarette is a cylindrical roll of tobacco material mass contained in a non-tobacco or paper wrapper. Machine manufactured cigarettes (15-20,000/min) can be found in 5-8 mm in diameter and 70 -100 mm in length, predominately with a 15-25 mm in length matching diameter cellulose acetate filter plug. This plug is wrapped with a porous wrap which is often coated with a silicone treated colored filter tipping paper.

The manufactured cigarette is a highly engineered device in which all physical elements of the cigarette are carefully controlled, such as packing density, particle size distribution (PSD), rag cut per inch (cpi), color appearance, resistance to draw (RTD), tobacco, and tobacco derived blend composition. The raw materials are predominately tobacco (*ca.* 50 % w/w) and materials derived from tobacco, but these materials are often augmented with cellulose fibers from wood pulp. The raw material, tobacco, is the source of nicotine, the cigarette structural support, and the source of the myriad of smoke components.

A. Raw Materials

Tobacco (*Nicotiana tobacum* and to a limited basis *N. rustica*) is like any other commercial agricultural product, and therefore needs to be controlled from seed germplasm to its incorporation into tobacco products. Unlike other agricultural products, however, tobacco in cigarettes is combusted into smoke that is laden with addictive nicotine, the fundamental basis of tobacco use and addiction. The control from the field to a cigarette is important as it affects the leaf characteristics, smoke chemistry, degree of combustibility and organoleptic properties. The growing of tobacco is a blend of art and science.

From seed germplasm to production and handling to manufacturing, the processes are robustly controlled to nominalize chemical composition variability. The agronomic practices are a determinant factor in botanical, physical and chemical properties of the initial biomaterial and the result of managed gene expression. Analysis of natural tobacco leaf has been shown to contain more than 3,000 endogenous plant organic and inorganic chemical compounds, such as organic acids, alcohols, aldehydes, ketones, quinones, alkaloids and bases, alkenes and alkyenes, amino acids, carbohydrates, esters, inorganic elements, N-heterocyclic compounds, phenols, sterols, oxygenated terpenes, isoprenes and related compounds.

Post harvest manipulation (curing) determines the ultimate physiology and biochemical character of the leaf stock used for product manufacturing and is considered a critical step in producing a standardized commercial product. Importantly, the nature of the biomaterial from which cigarettes are made is affected by the region in which it is produced, by the system of production, and by the curing method (air, sun, fire or flue-curing).

Nicotine biosynthesis is an independent biosynthetic pathway that begins in the roots and is conditioned on soil nitrogen content, nitrogen absorption and environmental conditions. The level of nicotine biosynthesis is controlled by two non-linked loci, Nic 1 (A) and Nic 2 (B). Commercial cultivars are homozygous dominant at both loci. All other nicotine alkaloids are derived from nicotine in various biosynthetic pathways. Overall nicotine concentration can be increased by genetic breeding or molecular biological techniques, such as anti-sense or promoter gene amplification or insertion, e.g. (Y-1), growth regulators and photoperiod. The overall concentration of nicotine in the plant leaf increases after topping and is distributed based on a stalk rank order basis (top to bottom) and tips to stalk base. Nicotine is known to evaporate from mature leaves and to have a toxic effect on insects on distant plants.

The level of nitrogen fertility has a direct positive correlation between leaf nitrogen and nicotine concentration. Nitrogen fertility has a direct effect on total alkaloids. Alkaloid concentrations in the plant leaves vary considerably and there is a descending rank order of concentration from the top of the cultivar leaf lamina to the roots. There is also a concentration gradient from the tip of the leaf to the base

The role of nitrogen in the soil has a direct affect on the formation of the potent tobacco specific N-Nitrosamines, the chemical reaction between $NaNO_2$ and nicotine (nitrosylation).

B. Tobacco Types

There are three specific types of tobacco that are used in the manufacture of a US Blended cigarette (USB):

1) Flue cured or sometimes referred to as fire cured, Virginia or bright tobacco. This type of tobacco is aged by using heat in the post harvest senescence period. This tobacco cultivar is characteristically moderate in nicotine and relatively high in natural sugar content.

2) Burley or air cured. This type of tobacco is ambient air cured in the post harvest senescence period. It is characteristically higher in nicotine and lower in sugar content.

3) Oriental tobacco grown in countries in the Mediterranean area such as, Yugoslavia, Greece, and Turkey. This tobacco is characteristically low in both nicotine and sugars but relatively high in volatile aromatic compounds.

In the USB cigarette there is an equal ratio on a weight-weight basis (w/w) of flue cured and burley but can be skewed in favor of either tobacco type or manipulation of the deliveries. This mixture accounts for *ca.* 50% w/w of the total mass of the cigarette tobacco column rod. Oriental tobacco makes up less than 5% w/w of the tobacco column rod. There can be large differences in chemistry based on leaf position. The upper third leaf position on both cultivars has the highest concentration of sugars and nicotine whereas the lower third stalk position has the lowest. The different biochemical characteristics of the leaf biomaterial afford the large

range of degrees of freedom in cigarette design and deliveries. Flue cured to burley ratios in a blend are a readily controllable parameter.

1. *Flue Cured Tobacco*

Flue cured (F/C) tobacco, which is sometimes referred as “Bright” or “Virginia” tobacco, derives its name from the unique manner in which the tobacco is cured with artificial heat in tightly controlled barns or sheds (5-7 days). F/C tobacco is unique because it is the only tobacco that goes through a controlled curing process of humidity and temperature control.

Curing is both a chemical and biological process affected by the temperature, humidity, air circulation and starting chemical character of the leaf stock. All other tobacco goes through ambient environmental curing spanning weeks. The "yellowing" stage is the most crucial biochemical aspect of curing where the green chlorophyll pigment is biodegraded to carotenoids pigments; complex carbohydrates (starch) are metabolized into free simple sugars; proteins are hydrolyzed into free amino acids (formation of Amadori/Mallard compounds with simple sugars); and there are changes in polyphenols, diterpenes and the nitrosylation of nicotine through the conversion of nitrate to nitrite (TSNA's).

Flue cured tobacco is broadly classified as to the country of origin, such as US, Brazil, Zimbabwe or China and then further classified as to region with each country. The ultimate use in the production may be for cigarettes, pipe, and cigars or as filler.

2. *Burley Tobacco*

Burley tobacco is a key component in the manufacturing of blended cigarettes both as a blend contributor but also as a filler tobacco. Its filler capacity is due to its open structure that readily accepts flavoring/casing materials (sauces) pivotal in lower delivering products and value-for-money/generic brands.

The curing of burley proceeds in three distinct stages and is like F/C in that curing is a complex biochemical process. The first stage, the "green stage," is the in-field wilting (2-5 days) where chlorophyll degrades (yellowing). The tobacco goes through two more stages; the "yellow stage" (5-10 weeks) and the final stage, the "brown stage." The latter two stages are in the open air curing barns. Temperature, humidity, air flow and sunlight control the curing process. However, these conditions are environmental conditions and therefore can be random and allow little control. These random ambient curing conditions can affect the curing process but also the present opportunity for microoflora growth particularly if moisture is a predominant environmental factor.

The biological activity of burley is greater than F/C which is greater than Oriental tobacco (discussed below). Combustion of burley tobacco produces more ammonia, benzo (a) pryrene, acetone, methyl ethyl ketone (MEK) and HCN than either F/C or Oriental tobacco and is most likely the largest contributing factor to blend biological activity.

3. *Oriental Tobacco*

Oriental tobacco is genetically linked to *N. tobacum* but extensively cultivated and grown in Mediterranean and Balkan regions. Oriental tobacco is highly aromatic but is a small cultivar with small leaves as compared to either burley or F/C tobacco. It size and biochemical character (aromatic) are due to the conditions in which the cultivar grows; poor soil quality and a stressful environment. Oriental tobacco was used traditionally in small quantities to smooth, to soften and to add aroma to US tobacco, F/C and burley blends. Today, Oriental tobacco is a mainstay of all US blended cigarettes.

There are three main types of Oriental tobacco; Izmir, Macedonian Basma, and Samsun (Bashi Bagli). Unlike F/C and burley tobacco, Oriental tobacco cultivars are not topped since

doing so alters the formation of aromatic compounds and leaf size. Oriental tobacco is hand picked (primed) from the bottom to the top of the stalk over the season and air dried by environmentally lowering the moisture in two stages on suspended cotton strings.

C. Combustion By-Products

When tobacco pyrolyzes it produces a myriad of semi-volatile, volatile and non-volatile compounds, such as PAH's, polynuclear hydrocarbons, azarenes, N-nitrosamines, aromatic amines, aldehydes, hydrazine, organic compounds of benzene, vinyl chloride, and a host of inorganic compounds such as nickel (Ni). arsenic (As), chromium (Cr), lead (Pb) cadmium (Cd) and polonium-210 (Po-210). All these as well as many more smoke components have been defined as carcinogenic in animals by IARC. In general, when proteins/amino acids are combusted they are converted into bases. On the other hand, carbohydrates/sugars are converted into acids whether they are natural to tobacco or an added substance.

1. *Free Radicals*

It is also noteworthy that cigarette pyrolysis produces smoke containing numerous free radicals that are a highly reactive chemical species. Free radicals can and do react with other chemical entities and therefore may react with other additives, and/or other pyrolytic products or living cells (DNA adducts).

There are two distinct types of free radicals; long lived in the particulate phase, and short lived in the vapor phase. Long lived free radicals are found in both main stream and side stream smoke condensates. They have been detected and quantified using electron spin resonance (ESR) spectroscopy at 1×10^{17} radicals/gram of tar or 4×10^{4} per puff with ESR signals spanning days. The postulated source of these long lived radicals are polymers of semi-quinone associated with quinone and hydroquinone groups and have live times in excess of 5 minutes. It

is also noteworthy that free radicals grow in number over time consistent with free radical propagation kinetics. Smoke free radicals have a steady state mechanism involving nitric oxide oxidation to nitrogen dioxide and then random reactions principally with smoke constituents, such as isoprene, butadiene, acrolein the combustion end product of the additive glycerol. Free radicals react with smoke olefins as well as other molecules with unsaturated carbon bonds or highly reactive oxygen-containing molecules produced and formed during the combustion process that cause DNA damage and the formation of DNA adducts.

The short lived radicals are somewhat problematic to analyze and quantify but can be done using an ESR spin trapping technique. There are 1×10^{16} radicals per cigarette or 5×10^{14} per puff with half lives in the order of seconds.

D. Overview of Manufacturing

Harvested tobacco goes through multiple manufacturing process steps after purchasing and prior to any cigarette manufacturing. The first such step occurs at the Green Leaf Threshing (GLT) processing plant, sometimes referred to as the Stemmery. The GLT plant removes the mid-rib and veins from the leaf to produce de-stemmed lamina. The stems that are removed are collected, packaged by size and used latter in the manufacturing process.

After removing the structural material (stems) from the leaf, the lamina is further processed in a redrying, bulking and blending process and then packed into "tersa" or "hogshead" bales for the next step of aging. The different types of tobacco are packed separately but there is a trend to prepare specific blend unit packaging. The controlled aging process last for several months with the intent to enhance smoking characteristics before the material is processed into cigarettes. During the aging process, the environmental conditions are controlled to avoid mold growth at 12-14% moisture content and 15 +/-5° C.

The cigarette manufacturing plant in divided into two distinct operating sections; primary and fabrication. Tobacco stock arriving at the "primary" side of the plant is at 12-14% moisture content. Each tobacco type is segregated and processed separately from different bulking bins until they are all combined to form the specific brand blend prior to cutting. The blending is determined by several parameters, such as leaf chemistry, and physical and organoleptic characteristics.

In the "primary" section, both F/C and burley tobacco are steam conditioned in a vacuum chamber. Oriental is not steam conditioned. Once the burley and F/C components of the blend are moisture equilibrated, casings are applied. Casings are complex mixtures of additives, such as DAP, sugars, cocoa, PEG, etc. contingent on blend formulas.

Burley is cased in large revolving cylinders and then goes through a re-drying process. The casing is then reapplied and then dried to about 20% moisture content. Burley can be re-dried as many as six times. Once the burley is cased and re-dried for the last time, the blend is reconstituted. F/C, on the other hand, only goes through one phase of casing due to its high intrinsic reducing sugar content and, like burley, is redryed to 20 % moisture content. The moisture of Oriental is adjusted to 20 %.

The next step is tobacco blend configuration where burley, F/C, Oriental and RECON are blended followed by cutting, reduction in moisture content (< 15%), and addition of "expanded tobacco" ("ET" see below) and application of final blend flavoring package in an alcohol carrier. Once completed, the rag is ready for pneumatic transport to the fabrication section of the plant for cigarette making, packaging and storage in a condition warehouse for equilibration prior to market distribution.

E. Reconstituted Tobacco (RECON)

The use of RECON is the one of the principal methods of introducing acid base ammonia chemistry and other additives into the USB non-menthol cigarette blend. RECON can be considered a chemical-additive delivery system in addition to the casing process of tobacco. Ammonia chemistry is utilized for several reasons; 1) to scavenge nicotine from each blend component; 2) to equalize the concentration of nicotine in the tobacco column rod; and 3) to modify pH such that nicotine becomes a free base. *Free nicotine*, which is controlled by smoke pH, is a more potent form of nicotine that is in the gas phase rather than bound nicotine that is in the particulate phase. The extensive use of ammonia chemistry in RECON converts the salt linked or protonated nicotine into "free" nicotine that has a higher potency than its salt/protonated form. Free nicotine it is not detected by the smoking machine analysis of tar and nicotine since it is in the gaseous state not in the particulate state of matter.

The primary importance of RECON is neither the utilization of manufacturing waste nor the enhancement of economy of manufacture. Rather, RECON is important because it introduces a significant amount of additives into the cigarette blend. These additives accomplish two distinct purposes: 1) they increase the addictive capacity of the cigarette and 2) they facilitate the ease of smoking by ameliorating the effects of inhaling smoke.

RECON tobacco comprises about 20-30% of a USB cigarette's blend formulation on a w/w basis. It is a chemically manipulated material using abundant additives, such as glycerol, licorice, cocoa, honey, polyethyleneglycol (PEG), simple sugars, invert sugars and ammonia based additives such as ammonium hydroxide, urea and diammonium hydrogen phosphate (DAP). The ammonia based additives in RECON play a key role in the manipulation of nicotine. The finished product is a highly energized chemical matrix which forms the basis of many of the chemical reactions occurring in the tobacco rod column, such as nicotine scavenging, generation

of free nicotine, smoke pH manipulation, and formation of some flavor reaction products.

1. *Raw material components and composition of RECON*

RECON is produced utilizing by numerous by-products of the cigarette manufacturing process. There are three (3) distinct RECON types; Paper I, Paper II and band cast. The raw material used to make RECON contains the following components:

1) *Offal or the tobacco dust* generated in either the Green Leaf Trashing (GLT) plant or in the Primary manufacturing process. The GLT Plant strips and removes the veins of the tobacco leaf into large strips of lamina and produces a by-product called stems. Stems can be utilized either as a cigarette blend component or as one of the sources of raw material for RECON.

2) The primary portion of the manufacturing plant produces the fines and winnowers when tobacco, a moisture sensitive biomaterial is moved rapidly through the manufacturing process, either pneumatically or via high-speed conveyor belts. This aspect of the manufacturing process causes dehydration and brittleness of the tobacco material, and therewith the formation of tobacco fines and dust (offal).

3) *Stems* produced at the GLT Plant

4) Tobacco fines or winnowers

5) *Product Reclaim*. Finished product that is collected from the distribution channel is returned to the manufacturing plant for reprocessing. This includes the finished goods that, due to moisture content loss, are deemed unsuitable for smoking due to increased irritation, harshness and the fact that they pose a fire hazard.

6) *Unique tobacco cultivars* are used either to augment nicotine content or to augment or enhance flavor attributes of the final RECON product.

7) Cellulosic material from wood pulp added for fiber content

When they leave the manufacturing plant, cigarettes are at *ca.* 14-14.5% moisture content (MC). This MC decreases at the rate of 0.5% per month until the MC reaches 10-11 % at which time they are collected and returned to the manufacturing plant for reutilization. Essentially, a finished product leaving the manufacturing plant has 6-8 months of shelf life contingent on ambient conditions. Large variations in temperature, humidity and storage conditions can greatly

affect the rate of moisture loss. The filter and tobacco rod column paper are mechanically removed and the original manufactured tobacco with all its additives are reclaimed. Non-menthol and menthol cigarette brands are processed separately.

2. *How is Paper RECON Made?*

There are two distinct types of paper RECON: Paper I and Paper II. The paper RECON is manufactured using the Schweitzer process and it is the same manufacturing process utilized in the manufacture of ordinary paper. The differentiating factor of the final RECON product depends on where in the EU the RECON will be used, and the specific country regulations on the types of additives that can be used in the manufacture of cigarettes. The main difference between Paper I and Paper II is the use of diammonium hydrogen phosphate (DAP). In some countries e.g. Germany, the use of DAP as an additive is prohibited.

a. Type I

Paper RECON is made by taking tobacco by-product materials and putting them through a process of repetitive hot water extraction until the residual material is white cellulosic pulp/fiber suspended in an aqueous medium. The extracted solubles are collected in a thermally controlled reaction vessel/vat where additives are combined and chemically reacted. This extracted solution is referred to as the “Mother Liquor” and it can be concentrated or diluted as required or specified in the manufacturing process.

The cellulosic pulp is poured onto a moving stainless steel (S/S) perforated belt which has a vacuum applied to the underside of this belt. The application of the vacuum facilitates the removal of the water and the formation of the paper sheet. Both the rate at which the cellulosic pulp is applied to the belt and the rate of dehydration control the basis weight of the formed sheet, i.e. the thickness.

The chemically reacted "Mother Liquor" is then reapplied to the partially dehydrated paper sheet at the terminus of the sheet formation process. The rate of application is also a controllable parameter in the final product. The two main controllable variables in this process are 1) the basis weight and 2) the chemically reacted "Mother Liquor" application rate. Both factors can determine the final chemical characteristics of the sheet product, such as nicotine or additive content. The product is dried and cut into irregular pieces and placed into a plastic lined container.

b. Type II

The only difference in paper RECON Type II product is that there is *NO* DAP added to the "Mother Liquor" in the reaction vessel/vat. Albeit, the same ammonia chemistry for which DAP is responsible is achieved through other means, i.e. by using ammonia and salts of organic acids.

The industry asserts that the water soluble components (mother liquor) that are extracted and separated during the manufacturing process and reapplied are not "ingredients/additives" added to RECON, but are materials/substances naturally intrinsic to the initial tobacco stock. This assertion is demonstrably untrue.

3. *Band cast reconstituted tobacco (Dark RECON)*

Band cast uses the same starting raw materials but differs fundamentally from the paper making RECON process. Unlike the paper process, band cast is made by adding the stock raw tobacco materials (see list above) and prescribed chemical additives into one reaction vessel. The tobacco material is then pulverized with the additives forming a thermally and chemically reacted slurry mixture. The sheet is made by pouring the slurry into a “doctor blade” which regulates the amount of slurry that is applied to a moving S/S non-perforated belt. The basis

weight can be controlled at this point.

The slurry mixture then goes through three separate heating zones where the water content is reduced forming a solid sheet. This solid sheet is then cut into irregular pieces and boxed in a similar manner to the paper RECON.

4. *Add-ons*

a. Expanded Tobacco

Expanded Tobacco (ET) is produced by use of either the ammonium carbonate (ACET) or the pressurized carbon dioxide expansion process. The expansion process "puffs" either stems or lamina utilizing the different states of matter of carbon dioxide at different temperatures and pressures. In the case of ACET, however, the thermal decomposition of ACET into carbon dioxide and ammonia is utilized to puff either stems or lamina. Both expanded stems and lamina are treated with casing sauces. Additives are also added to these forms of ET. In addition, the thermal decomposition of ACET results in the production of ammonia and carbon dixoide, and hence ACET is one of the means by which ammonia chemistry is achieved in tobacco products without the explicit use of ammonia.

b. Stems

There are two basic types of stems that are added to the blend, water treated stems (WTS) or shredded dry stems (SDS).

c. Shorts

Shorts are small tobacco fragments added to the blend that originate when the longer strands (tobacco rag) break down during the manufacturing process. The amounts and sizes of shorts (PSD) are controlled since the pressure drop, resistance to draw (RTD), combustion mechanics, and overall tobacco column density, are all affected by the dimension of the shorts.

II. INTENTIONAL ADDITIVES

The legal definition of the term “additive” is "any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any [food]; including any substance used in producing, manufacturing, packing, processing, transporting, preparing, treating, or holding [food]." There are two distinct classes of additives, namely intentional and unintentional. Intentional additives encompass *all* chemicals, substances, complex botanical extracts, flavorings, excipients, ingredients, inks, gums, combustion modifiers, aesthetic, inorganic salts or functional chemicals, etc., that are deliberately added to a traditional tobacco product or an engineered product, that is either combusted or heated. I define "product" as the entire offering of the tobacco device and its associated packaging. Thus, the tobacco product includes the inner foil wrapper, the paper container, the soft or hard pack in which the cigarettes are contained, the inks use to print the logo and trademark identifiers, and the outer protective film of the package.

Intentional additives can have a multitude of effects either individually or collectively; namely:

> 1) to enhance the addictive potency of nicotine either through blend scavenging, tobacco column equilibration, synergistic effects of pyrolysis products or shifts in pH;
>
> 2) to ameliorate the effects of smoke by making it more palatable either through the use of sweeteners or chemical agents that negate the normal airway aversion to smoke or have pharmacological action; and
>
> 3) to mimic or mute smoke's effects with adolescents (which can be intrinsically toxic in either the neat state or pyrolyzed state).

In the US, the industry uses 616 intentional chemical additives to blended cigarettes that either mask or ameliorate smoke or potentate the delivery and pharmacological effects of the addictive

substance, nicotine. Furthermore, there is a myriad of unintentional additives present in tobacco final products.

Key additives are those that are used as ameliorants (sugars, cocoa, and licorice 10% w/w), those that are used as enhancers of nicotine delivery and addiction (ammonia based, i.e. ammonium sulfide, DAP, ammonium hydroxide, ammonium citrate/tartrate, etc.), and thermally decomposable organic/inorganic compounds or other chemical combinations that produce the same chemical effect of a banned substance, such as DAP in Germany. Inorganic compounds such as sodium hydrogen carbonate and calcium carbonate are utilized as they thermally decompose into their respective oxides and, when in the presence of water, into a base.

A. The Industry's Treatment of Additives in the United States

In the United States, tobacco companies are protected from fully disclosing their ingredients to the public. Although the Federal Cigarette Labeling and Advertising Act (FCLAA) requires manufacturers to provide a list of cigarette ingredients to the Secretary of the Department of Health and Human Services (HHS), these lists are neither brand nor company specific.[1] Rather, the industry, with the help of the law firm of Covington and Burling (C&B), constructs a single list of ingredients based on volume and usage. In other words, after receiving each tobacco company's complete, non-branded list of all ingredients used in cigarettes, the law firm then constructs a "master" list which consolidates these individual lists and lists the ingredients by weight. It is this master list that is send to HHS. Even though this list is neither company nor brand specific, the FCLAA treats the information in these lists as "trade secret or confidential."[2] Thus, if the Secretary were to publicly disclose the information contained in the

[1] 15 U.S.C. §§ 1331-41 (2001)
[2] 15 U.S.C.A. § 1335a (2001)

list, he or she would be subject to a fine, imprisonment, or both, and would be removed from office.[3]

C&B's function is the collecting and consolidating all the additives from each company used from the prior year and listing them in rank order of total quantity used. The listing is due each year in March covering the prior year's usage. These lists do not provide any quantitative or safety assessment linkages between any additive or group of additives with any commercial brand, and therefore there is NO ability to make any health assessments or warnings. Under current US federal law, there are no requirements of the industry to disclose or test the additives in tobacco products.

B. The Industry's GRAS Argument

The tobacco industry claims that all of the additives used in the manufacture of cigarettes and other tobacco products are approved for use by either by the FDA GRAS list or the Flavor and Extract Manufacturers Association (FEMA) list.[4] The industry uses this "GRAS" argument to suppress both litigation and regulatory legislation concerning additives: if people believe that the industry uses only "safe" GRAS approved ingredients, then there will be no public pressure to disclose these ingredients. However, the GRAS argument is faulty and misleading as I explain below.

C. Why the GRAS Argument is Bogus

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[3] 18 U.S.C.A. § 1905 (2001) "(2)(A) Any information provided to the Secretary under subsection (a) of this section shall be treated as trade secret or confidential information subject to section 552(b)(4) of Title 5 and section 1905 of Title 18 and shall not be revealed, except as provided in paragraph (1), to any person other than those authorized by the Secretary in carrying out their official duties under this section. See 15 U.S.C. §§ 1335a(a), (b)(2)(A) & (B) (2001)."

[4] FEMA was formed in 1909 to ensure a substantial supply of safe flavor materials to the consumer. The key element of their mission is safe and wholesome flavors to enhance the appeal of foods, beverages and drugs. All are used expressly for ingested items and FEMA makes no claim for tobacco use(s). The FEMA Table and the GRAS Table are almost identical. Flavors not meeting the GRAS/FEMA positive list must be labeled "artificially flavored."

1. *Ingredients on the GRAS List were Never Intended to be Burned*

First, seemingly harmless ingredients such as licorice, imitation raspberry, chocolate, honey and brown sugar, are actually *harmful* when burned in conjunction with nicotine since the sugars in these ingredients create acetaldehyde when burned. The fact that chocolate, honey and brown sugar are harmful when burned in conjunction with nicotine is important since it demonstrates not only that seemingly harmless ingredients have the potential to harm when burned, but also that seemingly harmless ingredients have the potential to harm *when burned in conjunction with other ingredients*, such as nicotine. This demonstrates one of the main problems with the GRAS argument, namely, that the ingredients on the GRAS list were *never intended to be burned*. This is significant since chemicals undergo a molecular change when burned, and may be transformed into carcinogens as a result. Thus, although an additive may be approved for use in foods or toiletries, when pyrolyzed, a benign additive can be transformed into a biological toxicant/carcinogenic substance. Importantly, neither the GRAS nor the FEMA lists cover the use of the positive listing for use in any form of tobacco. Nor have any of the GRAS and FEMA positive listings been tested in tobacco, in a pyrolyzed state, or in conjunction with other pyrolyzed additives or tobacco. The industry has not tested any of its additives in any formal scientific manner consistent with due diligence or duty of care. Additives, in other words, have not been tested neat, or in conjunction with tobacco or other additives, in any scientifically accepted standardized toxicity protocols. Without this type of testing it is impossible to determine the toxicological effect of the single additive or the reaction product(s) on humans or provide adequate advice to the consumer. Therefore, although a tobacco ingredients may indeed appear on the GRAS list, this does not guarantee that this ingredient is safe.

a. How Additives Change During Pyrolysis

There are several pertinent examples of how additives change during the pyrolysis process.

i. *Sugars*

Sugars make up a major portion of additives contained in cigarettes. Simple sugars when pyrolyzed are converted into organic acids and subsequently into a variety of aldehydes. Of particular interest is the aldehyde, acetaldehyde, which intensifies the effect of nicotine on the brain and hence its addictive properties. Acetaldehyde-nicotine studies in animals demonstrate that animals tripled their self administration of nicotine in the presence of acetaldehyde. Even though acetaldehyde is not currently classified as a carcinogen, there is an abundance of animal and *in vitro* data supporting a classification of carcinogenicity. In addition, sugars are not listed anywhere in the FDA GRAS list. Caramel and invert sugars produce catechol. When heated, catechol produces a major known co-carcinogen in tobacco smoke. The Maillard reaction is responsible for the formation of caramel in the presence of amino acids or amines that can be derived from ammonia based additives or from complex mixtures of fruit extracts. Licorice (glycyrrhizic acid) can be reacted with ammonia to produce ammoniated glycyrrhizic acid.

ii. *Glycerol*

When pyrolyzed, Glycerol is converted to acrolein, a probable human carcinogen (Group C) and a ciliostatic agent in the lungs. Acrolein is a potent irritant, intensely chemically reactive and has acute toxicity. In a 1989 industry study, glycerol was found to cause increased cellular dysplasia in both acute and chronic animal inhalation studies. This glycerol study demonstrated aberrant cellular changes and hence that glycerol could be harmful to humans. The study was not fully completed because the industry was concerned about whether it could explain away the mounting negative data. This prompted RJR to begin replacing glycerol in their cigarette blends

with sorbitol, another substance that has humectant like properties.

iii. *Cocoa*

Cocoa contains at least 10 psychoactive compounds that may affect the bioavailability of nicotine by acting on the respiratory system or increasing the permeability through the lung epithelium or increasing the smoke pH. In addition, the combustion products of some of these compounds have MAO-I properties and may, when conjoined with flavor enhancers, contribute to the addiction of cigarette smoking.

2. Ingredients on the GRAS List Were Never Intended to be Inhaled

Another problem with the GRAS argument is that the ingredients on the GRAS list are not expected to be *inhaled*. Rather, the GRAS list applies to ingredients in foods or cosmetics --- substances that are ingested or topically applied. The fact that ingredients in cigarettes are inhaled and are not ingested or topically applied is significant. First, certain innocuous ingredients (such as cocoa) may actually dilate the airways, and therefore expose the body to more nicotine and higher levels of tar. Second, foods and cosmetics are "filtered" by the body's detoxification systems, whereas the lungs lack any detoxification system. Therefore, a chemical may be "safe" if applied or ingested because the body's detoxification systems disarms the potential harm that it may cause. But the very same chemical may be dangerous if inhaled through the lungs. It is important to keep in mind that the approval of food additives (see addendum for the classification of these additives) is based on a judiciously applied assumption that substances of related chemical structure are assumed to have the same freedom from the possibility of adverse effects. But the very same chemical may be dangerous if inhaled through the lungs, since the lungs lack the capacity to disarm the potential of this chemical to do harm. The ingredients on the GRAS/FEMA lists have NEVER been approved for use in products that

are pyrolyzed and inhaled directly into the body with unlimited access to virtually any organ system.

a. Biodetoxification Systems: The Body vs. The Lungs

The fact that the additives/ingredients/flavorings that appear on the GRAS/FEMA Tables are designated to be used in foods and cosmetics/toiletries is important because ingredients that are ingested have a unique and different effect on the body than ingredients that are pyrolyzed and then inhaled. The biochemical digestion process of the approved additives has multiple opportunities to be detoxified in the body's biochemical systems through biotransformation and biodetoxification. The body's digestive enzymes hydrolyze compounds such as esters, acetals, lactones, and glycosides. In the lungs, on the other hand, these same chemical reactions do not occur. This is because unlike the lungs, the body, through its biochemical systems, is able to distinguish different types of toxic substances based on their "functional groups" (i.e., the complex molecular structure that is characteristic of each chemical). For example, the body will metabolize a molecular structure known as an "aliphatic chain" more efficiently than it will metabolize a more complex structure known as an "aromatic ring." This is because the former structure comprises a straight chain of saturated chemical bonds, whereas the latter structure is a cyclical chain of unsaturated chemical bonds. The lungs, however, not only lack the discriminatory capacity possessed by the body's detoxification system, even worse, the lungs lack *any* capacity to identify the molecular structure of a toxic substance. Whereas the body has a variety of detoxification processes which correspond to the various molecular structures found in toxic substances, the lungs have none. When introduced into the body, a toxic substance will meet with biochemical defenses, but when introduced into the lungs, a toxic substance will inevitably inflict damage, since the lungs have no defenses at all. The lungs are a "chink" in the

body's "armor" and once a toxic substance gets through this chink, it wreaks maximum damage by going directly into the bloodstream, and ultimately to the heart and the brain. Therefore, pyrolyzed additives or intact transferred additives are not biotransformed or biodetoxified in the same manner as with the process of ingestion and subsequent digestion. Biodetoxification systems make substances less toxic to the body and less likely to cause human biotoxicity. Unfortunately, the lungs lack biodetoxification systems.

Because tobacco additives are not rendered less toxic by the normal biochemical processes of the body, the industry's insistence that their ingredients should not be disclosed and their argument that the ingredients in tobacco products are safe because they appear on the GRAS or the FEMA lists, jointly contribute to the public's misunderstanding about tobacco products. In addition, the industry's assertion that ingredients in their products are safe because they are either GRAS or FEMA approved, does not account for any of the pyrosynthetic reactions of the additive or their pyrolytic breakdown products.

Since the industry does not provide precisely what levels of additives are used in its branded cigarettes it is impossible for anyone, whether it be governmental health agency or the public, to evaluate judiciously the exposure levels of what might pass into a smoker's lungs. In addition, the asserted inferred health claim is not substantiated by any reasonable bio-toxicity studies that support the claim of human safety when inhaled with other additives and tobacco smoke. Lastly, the industry has not fulfilled its regulatory duty to obtain approval for the additives it uses in the production of its tobacco products. Some of the key elements of this approval are: data and information establishing "safety," intended technical effect, conditions of proposed use, identity, toxicological considerations, chemical composition, and literature search.

D. Other Additives

1. *Urea*

Urea as a tobacco additive that is used as a casing and part of the RECON manufacture. It has been shown to increase smoke pH and extractable nicotine deliveries but also reduces acetaldehyde concentrations. There is some indication that urea can reduce the polynuclear aromatic hydrocarbon (PAH) fraction in smoke. Urea is an additive used to add ammonia to the tobacco or RECON when pyrolyzed decomposes to cyanic acid (HNCO) and into CO_2 and NH_3. The cyanic acid is highly toxic, a lacrimator and a vesicant.

Other additives act as processing or aesthetic aids in the manufacture of the product, such as lip release silicones on the filter tipping paper, the combustion modifiers applied (potassium/sodium citrates) to the tobacco column paper or tobacco itself; adhesives for the tobacco column seam or filter annealing adhesives/polymerizing agents (e.g. triacetin); whitening agents (Titanium oxide) for the tobacco column paper or the pheromone Kabat that prevents tobacco beetle reproduction during storage of raw tobacco. Let us then turn to a discussion about these unintentional additives.

III. UNINTENTIONAL ADDITIVES

Unintentional additives have NO specific purpose but are by-products of the tobacco growing, handling and manufacturing processes.

The tobacco biomaterial carries with it numerous unintended materials, substances, chemicals, and by-products of its agronomic, manufacturing and handling processes. These residues can present incremental harm to the smoking user. There are microorganisms, insect and animal parts, foreign materials and other toxic entities. They include such substances as nitrate or lead incorporated into the plants from soil high in these substances/chemicals, fungal and bacterial metabolites, conveyor belt fragments, oil from the machinery, etc. Many of these

organism's endospores are activated with moisture *ca.* 20% and can ferment the additives into potent toxins, called aflotoxins. In addition, such species as *Bacillus* subtilis, *Aspergillis* niger and other microbiological organisms (molds, bacteria, fungi, protozoa, arthropods and nematodes) can be included and have been found in the tobacco final product. All of these materials and substances are entered into the tobacco erroneously and can increase the harm of a tobacco product.

Unintentional/indirect additives are basically the contaminants or substances that can become a part of the product during production, processing and storage generally owing to natural processes. Spotting, a discolored section of the tobacco rod paper, is the result of active microbiological fermentation.

A. Agronomic Microorganisms

1. The Genus *Bacillus*

Prokaryotic organisms in the soil are diverse and abundant. Of particular interest is the Genus *Bacillus.* This genus is predominately found in the soil, sewage, fecal material and diseased animals. One of the key distinguishable characteristics of this family is its ability to produce endospores which can exist within a vegetative cell (sporangium) or free spore. The thermal resistance of the endospores is of interest and they can be readily detected when tobacco is hydrated at 18-20% moisture content and in an ideal growth medium. B. subtilis is the most studied species.

Tobacco finished products carry with it the typical Bacillus taxonomy of soil bacteria, such as *B.* cereus, *B.* thuringiensis, *B.* subtilis, *B.* anthracis, etc. There are some 40 recognized species listed in *Bergey's Manual of Systematic Bacteriology.* Medium rich in glucose, KH_2PO_4, amino acids provide an ideal environment for growth.

The Bacillus species has specific non-medical (plant) and insect pathogenicity, and human medical pathology. For example, B. cereus causes a noninfectious disorder in the tobacco cultivar called "Frenching." Frenching is caused by an organic toxin produced by *B.* cereus which alters biological, chemical and genetic systems of the tobacco cultivar. One particular biochemical outcome of Frenching is the high concentration in the tobacco leaf of the amino acid L-isoleucine. In addition both *B.* anthracis and *B.* cereus are human and animal pathogens.

Bacillus species, such as *B.* popilliae and *B.* thuringiesis are all insect pathogens and have been intimately linked to insect diseases via *in vivo* sporulation and production of a delta-endotoxin (crystal toxin, a normal component of the spore coat) and it shares a striking similarity with toxins produced by *Clostridium* botulinum and C. perfringens.

Of the 40 species of the genus *Bacillus*, the two (2) of the greatest medical importance are *B.* anthracis and *B.* cereus. The former is widely known as the causative agent of anthrax. Albeit, *B.* cereus strains cause two (2) main types food poisoning as well as some of the other nonanthrax *Bacillus* species. The food poisoning by strains of *B.* cereus resembles food poisoning caused by *C.* perfringes.

The eye is the organ most commonly infected by nonanthrax *Bacillus*. This species causes pathology to the eye, such as endophthalmitis or panophthalmitis. The *Bacillus* species demonstrates unique kinship with other nonsporeforming species, such as *Staphylococcus*.

2. The Genus *Clostridium*

The principal habitat for the species *Clostridium* is soil. It is also a spore former with significant pathogenic effects in humans such as food poisoning, the necrotizing of body tissues, and interfering with nerve transmission due to its lethal alpha toxin. The species *Clostridium*

exhibits a pronounced intolerance towards oxygen.

The species *C.* tetani, *C.* sordellii, *C.*perfringens, *C.* histolyticum, *C.* difficile and *C.* novyi are the most recognizable and substantive species in human and animal pathology.

3. Fungi: *Aspergillus*

Fungi are aerobic microscopic organisms that grow as long threads or strands called hyphae. Soil fungi are grouped according to their biochemical mechanisms for securing energy. These groups are: saprophytic, mycorrhizal, and pathogens or parasites. The primary soil fungi are *Aspergillus* flavus, *A.* niger, and *A.* parasiticus are saprophytes. These fungi are found world wide but are more common in tropical regions where there are extremes of rainfall, temperature and humidity. In addition, the genus *Aspergillus* is characterized by the production of non-septate condispores which form spore-producing cells.

Fungi produce toxic metabolites called mycotoxins. According to FAO estimates, 25% of the world crops are affected by mycotoxins each year, including tobacco crops. Aflatoxins are potent biochemical metabolites that are considered carcinogenic, mutagenic, immunosuppressive and cellular toxicants. There have been eighteen (18) different types of aflatoxins identified. Aflatoxins are difuranocoumarins and divided into cyclopentenone and lactone series. Aflatoxins display potency of toxicity, carcinogenicity, mutagenicity in the order of B1>B2>G2 as illustrated by their LD50 values.

Afllatoxins are stable to heat up to their melting point (237-289° C). Major Aflatoxins are classified as:

1. Aflatoxin B1 & B2, produced by *A.*flavus and *A.* parasiticus
2. Aflatoxin G1 & G 2, produced by *A.* parasiticus
3. Aflatoxin M1, metabolite produced by biochemical processing B1 in humans/animals and
4. Aflatoxicol

NO animal species is immune to the acute effects of aflatoxin called aflatoxicosis or mycotoxicosis. The primary pathology is acute necrosis, cirrhosis and carcinoma of the liver exhibited by hemorrhage, edema, alteration in digestion and absorption and/or metabolism of nutrients.

Aflatoxins have been found in tobacco particularly with humid (moist) and warm storage conditions associated with tobacco in tropical countries such as Brazil and Zimbabwe. The FDA regulates the concentration of aflatoxins in food products and prohibits interstate shipment at concentrations >20 ppm (except for milk at 0.5 ppm).

The USDA has identified the species of *Aspergillus* as capable of producing aflatoxins in tobacco and 1997 RJR has an acknowledged that aflatoxins can be present in flue cured tobacco stocks.

4. Other Microorganisms.

In addition to the aforementioned microorganisms, nematodes, protozoa and arthropods are all found in cigarettes.

Nematodes are non-segmented worms (5mm) are responsible for a host of plant diseases. The class of most interest is the root-feeders that are concentrated around the roots of stressed or susceptible plants. This class of nematodes is a plant parasite and requires in-field treatment with agronomic biocide agents that prevent their action on plant yields.

Protozoa work symbiotically with nematodes to control bacteria, their principal food source. They are 5-500 mm in size. Arthropods can be carried over into the final product. They are normally desiccated and are consumed during pyrolysis.

B. Pesticide/Herbicide/Insecticide/Suckercide Residues

Tobacco is the most widely grown nonfood crop in the world by 117 countries and 33

million farmers. Weed control is an important factor in tobacco quality and yield and therefore requires the use of herbicides and field rotation due to the development of resistant weeds.

Tobacco production is like other agronomic crops in that it requires intervention with harmful organisms. The application of pesticides is not without its issues including the non-intended and non-beneficial effects on other plants, animals, and on the environment. The use of Good Agricultural Practices (GAP) and Integrated Pest Management (IPM) in developed countries is part of the agricultural system.

There are a number of international bodies seeking harmonization of the use of pesticides, such as World Health organization (WHO), Food and Agricultural Organization (FAO) and the EU. Most countries require a formal approval process for pesticides. However there is sporadic enforcement of MRL's, labeling, packaging and application procedures. In 1985 and amended in 1989, the International Code of Conduct on the Distribution and Use of Pesticides (Code) was published by FAO which detailed voluntary standards on the manufacturing, distribution, marketing and use of pesticides. The amended Code provides for a ban on organic chemicals, such as organochlorine pesticides aldrin, dieldrin, endrin and DDT. It is important to note that the Code is voluntary and only operates when countries have the infrastructure to manage the overall pesticide regulatory process.

Both the USEPA and the EU have established agencies, regulations, re-registration process for pesticides pre-1988. Albeit, there are a significant number of pesticides that are used on tobacco in the US that have not been re-registered, such as monocrotophos, fensulfothion, azinphos-methyl, malathion, diazonon, aldicarb, carbofuran, endosulfan and metholmyl.

The EU Council Directive of July 1991 establishes a community wide system for controlling plant protection chemicals. The objective of this Directive is to establish an

authorized active list (Annex I).

In spite of the initiatives of FAO, Code of Conduct, WHO and USEPA, there are substantive discrepancies in the harmonization on pesticide control, especially in less developed countries where pesticide control is still in its embryonic state. More than 40% of these countries lack rudimentary pesticide control practices.

There is an absolute need to have pesticide residues quantified in both raw material and finished product. In addition, the amount of an active ingredient that can be consumed daily (ADI), No Observed Effect level (NOEL), Maximum Residue Levels (MRL), Theoretical Maximum Daily Intake (TMDI) values and standard toxicological assessments inclusive of acute and chronic inhalation studies, adverse morphology, development, growth, life span, biochemical parameters and functional capacity, all need to be developed and published.

Current MRL's are not based on robust scientific or technical data. Currently, many MRL's are set by historical data from the individual country and are governed by distinctly divergent national regulations. This inconsistency contributes to highly variable values for the same pesticide residue on tobacco of different national origins.

1. *Maleic Hydrazide/Suckercides*

Maleic Hydrazide (MH) is a systemic suckercide used on both burley and flue cured tobacco cultivars. In addition to the systemic suckercide, MH, there are also contact/local suckercides. The suckercides prevent cell division in the meristem tissues of the plant and act like growth regulators.

Contact suckercides are fatty acid alcohols, such as n-octanol, n-deconal and mixtures of both. They are spray-applied to the stalk of the top three axils of the plant and affect both membrane and meristem tissues thus preventing the succulent sucker buds from growing. In

addition, there are other contact-local systemic agents, such as the dinitroanalines (flumetralin, butralin, pendimethalin and chloropham). The use of these agents has caused substantial soil resistant carry-over. The residues are higher in burley tobacco than in flue cured.

Maleic hyrdrazide (MH) is a true systemic agent and is the most controversial chemical utilized in tobacco sucker control. Its use is automated rather than being manually applied, like other agents. MH is known to affect the biochemical pathways in tobacco by increasing the concentration of reducing sugars, by decreasing the concentration of nicotine, by reducing the filling power and ash content, and by altering the equilibrium moisture content. All of the aforementioned disturb smoke chemistry.

Concentrations of MH residues are the highest of any pesticide used in the production of tobacco and are the most variable. MH concentration is not altered either by air or flue cuing processes and there is no deterioration upon storage. The concentration of recently cured tobacco leaves can serve as a reliable indicator of levels at all stages of trade in unblended leaf. MH levels are 35-94 mg/kg where 50mg/kg is a guideline level. The use of MH has escalated primarily due to its ability to be applied in automated manner as a suckering agent; thereby reducing labor content of the field production costs.

Blending processes will dilute the concentration of MH both in the cigarette rod and in the smoke. MH concentrations are highest in cigarettes when compared to other tobacco products, such as chewing, snuff or small cigars. MH (CAS # 123-33-1) is highly toxic to humans. The toxicity to humans is pervasive and includes carcinogenicity, reproductive and developmental toxicity, and neurotoxicity. MH has not been listed on the IRAC or NTP listing of carcinogens.

2. *Ethylenebisdithiocarbamate (EDBC)*

EDBC is a potent insecticide with its mechanism of action similar to the organophosphates. EDBC is a thiocarbamate which thermally decomposes to ethylenethiourea (ETU) a potent carcinogen. In addition, ETU has been linked to goitrogenic effects and hepatic tumors and suppression of the bone marrow.

EDBC is not advised to be used in application to food crops because of the toxicity of ETU.

3. *Systemic Insecticides (SI)*

A variety of pyrethroid and pyrethrins (organophosphates) are used for insect control. The production of dark fire cured tobacco relies heavily on the use of insecticides.

a. Methoprene (Kabat)

Methoprene is an insect growth regulator/hormone (IGR). It acts by preventing the insect development beyond the larval stage. In particular, methoprene is used to control tobacco beetle infestation in tobacco stocks no matter where they are stored. The female beetle produces about 100 eggs which are deposited on or near the tobacco supply. The eggs hatch in 6-10 days to produce wormlike larvae that are over stimulated with a juvenile hormone mimic. Methoprene has little or no effect on mature insects and has a half life of three (3) to seven (7) weeks.

Methoprene is a relatively non-toxic pesticide when ingested or inhaled but slightly toxic by dermal absorption. No overt signs of poisoning have been reported in incidents involving accidental human exposure to the single pesticide entity but studies in combination with other chemical agents have not been investigated.

b. Phosphene

In addition to methoprene, gas fumigation is used to control insect and rodent pests. Fumigants are gases that penetrate into all parts of the tobacco mass and possess a 100% kill rate

to biological systems undergoing oxidative respiration. The principal fumigant used is phosphine gas. Phosphine (phosphane) is an extremely flammable and explosive gas will kill all life forms. It has a garlic or fish like odor. Phosphine is produced in the chemical reaction of water with either aluminum or magnesium phosphide. There are chemical residue by-products of either aluminum or magnesium hydroxide from the reaction as well as ammonia and phosphoric acid.

Phosphine apparently does not directly affect the integrity of the biomaterial when it is applied to during the fumigation. However, un-reacted metallic phosphides demonstrate systemic toxic effects. Prior to phosphine, methyl bromide was used but it has been banned. Because of over use of phosphine, there are high levels of resistance to this toxic chemical in many countries of Asia and Australia.

C. Elements and Heavy Metals

In 1986 the Chernobyl nuclear reactor disintegrated with the release of several radioelements that have been shown to cause thyroid cancer as well as lymphoma and leukemias.

D. Foreign Materials

Tobacco that is harvested and placed in the auction system in the US frequently contains numerous large foreign materials, such as metal, cardboard, styrofoam, wood fragments, small animals, insects, latex rubber gloves, etc.

A majority of these materials are removed in the Green Leaf Threshing plant (GLT) sorting process, either through visual or optical recognitions systems or through magnetic sorters. However, many small fragments continue through the process and make their way to the cigarette manufacturing plant where they can ultimately make their way into finished product.

When one reviews the consumer complaints, and the corresponding chemical and optical

analytical processes that are conducted pursuant to these complaints, there is evidence that foreign materials make their way into final product. These materials produce an unpleasant organoleptic sensory response and a physical distress such as nausea, vomiting, headache, and severe irritation beyond that of usual and customary smoking. Material such as tobacco beetles, rubber parts from the conveyor belts in the manufacturing plant, latex rubber glove fragments, styrofoam and polyurethane from insulation materials are found in the samples.

E. Other Extraneous Hazardous Chemicals

Extraneous hazardous materials can emanate from multiple sources, such as cigarette packing, filter stock, recycled raw materials, environmental elements and/or genetic modification of the cultivar. Cigarette packaging that uses organic solvent based inks to label the cigarette rod and to print brand name logos on the intimate packaging of cigarettes is problematic when these chemical entities migrate from the packaging labeling material into the cigarette rod tobacco and are ultimately transferred into the inhaled smoke stream. This is particularly relevant when the mass of the packaging is equal or greater than the cumulative mass of the tobacco column and the protective wrapper is impermeable, as are Mylar and the other barrier wrapper materials.

The phenomenon is an issue especially with ultra slim cigarettes, such as Capri or Virginia Super Slims (15-19 mm circumference cigarettes) where the tobacco mass to packaging mass ratios are less than 1.

Solvent migration can be mitigated by the application negative pressure to packaging materials prior to use and banning the use of organic solvent based inks. Organic solvent based inks can be replaced solely with aqueous solvent based inks

Environmental solvent migration is an issue when cigarette packs or cartons are stored in environments containing organic solvents and there is reverse migration of organic solvents

through a permeable outer wrapper.

When recycled paper materials are used in the production of cigarettes, especially generic price point sensitive products, there is an issue of carry-over solvents from the use of printing materials that have used organic solvent based inks in the original printing of these materials (e.g., newspapers). Dioxin is such a chemical entity that has been identified in the stock of the cigarette rod paper

Dioxin is incorporated into "value for money" (lower cost products) cigarettes as a result of using recycled paper to produce the cigarette tobacco rod paper. It is a carry over from the recycling process particularly when organic based inks are used in the paper printing process. Dioxin has been listed in the 10th ROC as "having no safe dose or threshold below which Dioxin will NOT cause cancer." Premium priced cigarettes utilize virgin flax as the source of cigarette rod paper.

In addition, benzene, toluene and other organic solvents that are used in the printing process of cigarette packaging, carry over and migrate into the cigarettes contained in the cellophane encased package.

Genetically modified tobacco cultivars that have been produced by either genetic breeding (crosses) or transgenic genetic engineering present some unique issues, especially when viral, insect or bacterial resistance is introduced into the genetic/phenotypic make up of the cultivar.

Genetic cross breeding technology utilizes extant cultivars that have unique characteristics that can enhance a new cultivar's agronomic values, such as disease resistance, yield and quality improvements which are a composite expression of several components. Yield and quality generally refer to: number of leaves, leaf thickness, venation and physical properties

of color, size, structure, oil uniformity and injury tolerance.

The use of biotechnology to alter a cultivar's characteristics is an emerging science that overcomes the restraints of tradition breeding techniques. The sources of genes are tobacco itself and transgenic systems, such as bacteria.

In order to use genetic engineering techniques, the tobacco genome must be mapped and genotypic to phenotypic links elucidated. There are approximately 60,000 structural genes expressed in tobacco.

There are sophisticated molecular biological techniques that afford this information, such as restriction fragment length polymorphism (RFLP), random amplified polymorphic DNA (RAPD), amplified fragment length polymorphism (AFLP) and simple sequence repeats (SSR). The technique of transformation allows the introduction and expression of foreign genes.

It is the technique of transformation that generates the most concern. The source's genetic material is from prokaryotic biologic organisms, such as *Agrobacterium*, *E.*coli, *Brassica* napu, *B.* Thuringiesis, *Heliothis* virescens, and *P.* syringae. The transgene in tobacco produces toxins that are extrinsic to the native cultivar. These genetically induced toxins serve to convey insecticidal, herbicidal, nematodcidal, fungicidal and bacterialcidal actions and resistance, viral diseases (TMV) and physiological stress tolerance.

The alteration of the biochemical pathways that produce the toxins that provides resistance to tobacco pathogens has not been toxicologically assessed and may pose additional human health risks. Y-1 tobacco, a product of genetic manipulation to produce a cultivar that increased its nicotine content on a w/w % basis, was such a cultivar. The incorporation of Y-1 tobaccos into extant products was never conveyed to the public. Y-1 was to have transgenic disease resistance incorporated into its genetic make-up.

IV. CONCLUSIONS

Both intentional and unintentional additives are ubiquitous in tobacco products. Yet, there is a nominal understanding of their role in toxicity, of their impact on addiction, and of their pharmacological effects. This lack of understanding is fundamentally due to the industry's strategy, buttressed with the help of industry lawyers, to portray the disclosure of additives as both scientifically superfluous and legally objectionable. Fortunately, the WHO recognizes that more information about additives in order to effectively address the health concerns posed by tobacco products. While the WHO provides an excellent starting point in addressing the health concerns posed by additives, a comprehensive regulatory regime needs to include the following elements:

1) full quantitative disclosure of **all** the additives , including unintentional additives (such as pesticide residues and other contaminates) in a given tobacco product by name, brand and type with all the associated toxicological data; and

2) an accepted robust testing methodology of the additive which will provide the basis for restricted, limited, or permitted use at a specific quantitative level per tobacco product; and

3) the classification of each additive based on the biochemical structure that follows the FDA GRAS substance classification system, viz.:

Class I
compounds of simple organic structure metabolized through known biochemical pathways without adverse biochemical, physiological or pharmacological effect;

Class II
compounds structurally analogous to Class I but are generally synthetic and can be **reasonably assumed** not to have the aforementioned adverse effects;

Class III
compounds with structures inherently different from I and II in which reasonable assumptions regarding metabolic fate and freedom from possibility of adverse effects is precluded; and

4) limitation of microflora content to less than 10^5/cc; and

5) the identification, quanitification and marginalization of additives that produce free radicals.

In addition, the industry should be legally mandated to:

1) disclose the pharmacological effects of all additives in all tobacco products (including roll-your-own, moist snuff, etc.); and

2) disclose all unintentional additives, such as pesticide residues and other contaminates that are incorporated into the products; and

3) disclose all adverse findings on established additives; and

4) disclose evidence that relatively benign additives can be used as substitutes for additives known to be more dangerous; and

5) disclose information about the role of additives and filter design in particle aerosol physics.

RESEARCH

I. Rationalization of complex additive mixtures
- A) Concentration v. pharmacological effects
- B) Thermal additives
- C) pH manipulation
  - 1) *Ammonia based*
  - 2) *Strong bases*

II. Cellulose acetate/biodegradable filters
- A) Residuals (acetic anhydride/acetic acid/triacetin)
- B) Novel filter fragmentation

III. Effects of changing physical characteristics in conjunction with additives
- A) Cigarette length/circumference
- B) Tobacco material biomass
- C) PSD/cpi
- D) Open/closed pressure drop
- E) Reduced ignition propensity
- F) Tobacco rod ventilation/permeability/basis weight
- G) Distribution in smoke
  - 1) *particle phase*
  - 2) *gas phase*
  - 3) *bi-phasic*
  - 4) *semi-volatile*
- H) Effects of product aging

IV. Puff by puff analysis

V. Effects of non-intentional (contaminant) additives
- A) Agronomic
- B) Packaging
- C) Environmental migration

VI. Role of humectants in the formation of smoke aerosols
- A) Particle coalescence

VII. Duty of Care of Toxicological Additive Testing
- A) Neat
  - 1) Purity of Additive (USP)
  - 2) Complexity of Additive
  - 3) Homogenous Chemical Compound
  - 4) Complex Botanical Extract
  - 5) Synthetic Compounds (Menthol)
- B) In Combination with other Additive Components
- C) In Combination with Tobacco
- D) NTP Protocol
  - 1) Tiered Testing
    - a. in-vitro
    - b. in-vivo

VIII. FDA Food Additive Protocol (See Addendum)

ADDENDUM

FOOD and DRUG ADMINISTRATION
GUIDELINES for SAFETY ASSESSMENT of DIRECT FOOD ADDITIVES and COLOR ADDITIVES in FOODS

- Acute Oral Toxicity Studies
- Short-term Oral Toxicity Studies
- Sub-chronic Oral Toxicity Studies
- Chronic Toxicity Studies
- Carcinogenicity Studies
- Reproduction Studies
- Teratogenicity Testing in Rat, Mouse, Hamster and Rabbit
- Absorption, Distribution, Metabolism and Elimination Studies
- Short-term Tests
    - Ames Test
    - L517BY Mouse Lymphoma test
    - Unscheduled DNA Synthesis
    - Mammalian Cell Transformation Test
    - Sex-linked Recessive Lethal Mutation Test

OTHER Relevant Methodologies

- Testing in Multiple Species
- Chronic Inhalation Studies
- Bromo-deoxy uridine Labeling
- DNA Adduct Formation
- Cell Smoke Exposure
- NEAT Studies
- Chronic Skin Painting
- *in vivo* Genetox Testing