The History of the Safety Evaluation of Flavor Ingredients

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Introduction

This presentation document was written to educate students on the history of flavor safety evaluation. The idea to present this information to University level students stemmed from the concern that the general public is not adequately educated on flavor safety, in part, because they are not direct customers of the industry. This presentation will provide a background on the mechanism for determining the safety of flavors, as well as an interactive approach to seeing, smelling, and evaluating natural and artificial flavors. Throughout this presentation, we will reference the PowerPoint slides that accompany this document, which is also available as Supplementary Material.

We begin with a brief history detailing the primary challenge to the Food Additives Industry dating back to 1958. We will then see how the Flavor Industry, in cooperation with the U.S. Food and Drug Administration (FDA) designed a program to ensure consumer safety and confidence in the flavors added to food.

We will look at a few flavor ingredients in more detail and consider how it is that chemical structure relates to how they are processed by and interact with the human body when they are consumed as part of food—and how these considerations have been used to design a flavor safety program. Throughout this talk we will evaluate the aroma of a variety of ingredients that are found in foods consumed every day. There are photos taken in factories from all over the world so you can view how essential oils are produced.

Knowledge of the safety of flavor ingredients used in foods requires an understanding of the regulatory authority to use food ingredients.

But before we address the issue of food ingredients, a short history lesson is in order.

History

An Act of Congress is legislation enacted by the passing of identical Resolutions or Bills by the majority of members of both the House of Representatives and the Senate. The Bill is then sent to the President for his assent and signature. Only if the President signs the Bill within 10 days, does the Bill become law.

In 1938, President Franklin Roosevelt signed the Federal, Food, Drug, and Cosmetic Act giving authority to the FDA to oversee the safety of food, drugs and cosmetics. This new Act replaced the Pure Food and Drug Act of 1906.

Fast forward twenty years from 1938 to 1958 and it became clear that the 1938 Act needed to be strengthened and as a result Congress passed the Food Additive Amendment to the U.S. Food, Drug, and Cosmetic Act of 1958. Throughout this discussion we will be using the acronym FAA when referring to the Food Additive Amendment.

For the FDA and the manufacturers of food ingredients, including food flavors, the FAA changed everything. The reason was that the amendment required pre-market approval of all food additives by the FDA, meaning that food additives must be shown to be safe before they can be added to food. And what does safe mean? The FDA defines “safe” as a reasonable certainty that a food additive will cause no harm in the opinion of competent scientists. Notice that this is not an absolute standard but a standard that calls for reasonable certainty.

A food additive was defined as “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…if such substance is not generally recognized**,** among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures, (… or experience based on common use in food) to be safe under conditions of intended use…" (21 U.S.C. Sec 321 (s) 1988)

Think about what those words mean—GRAS substances, that is, substances that are generally recognized as safe, were considered outside the scope of food additives and therefore did not require FDA premarketing approval.

As students and scientists interested in either understanding or having a career in the Food Industry, you will come across the acronym GRAS all the time, possibly daily. If you take anything away from this presentation, every time you hear somebody discuss GRAS, in your head, finish the term with the phrase "under conditions of intended use". Keep in mind that the most important tenet of GRAS determinations is that it is only the specific use of the substance – it's specified conditions of intended use – that is GRAS and not the substance itself. In other words, a substance that is GRAS for use as a flavor is not GRAS for use as a sweetener or for any other non-flavor use.

Spearmint oil

Did you know that spearmint oil is GRAS? In your mind you just filled in, "under conditions of intended use." Why was the exemption granted for products that were GRAS *under conditions of intended use* and not simply GRAS? The answer is, risk is dose dependent. While I'm not a toxicologist—it certainly is true that the most frequently quoted maxim of toxicology is: "the dose makes the poison." What this means is, a harmless sprinkle of salt, flavors food; while too much salt can kill.

Since spearmint oil is GRAS, let's evaluate spearmint oil. Spearmint is an essential oil that is characterized by the aroma of its primary component, laevo carvone. Laevo carvone is an aroma chemical found in spearmint oil at a level of over 60%. It is very spearminty.

What is an essential oil? It is the volatile product obtained by distillation or expression from plant material of a single botanical form and species. Spearmint oil is produced by distilling spearmint leaves. There are many farms in the Pacific Northwest that grow both spearmint and peppermint. The process is typical of the process for all essential oils produced by distillation. The steam distillation process is pictured in PowerPoint slides 11 to 15.

Most essential oils are produced by distilling the botanical from which they are derived. Another method of production is expression. We will look at that process, later.

Do we think spearmint is safe? Spearmint is easily grown in most gardens in the United States. By itself, it can be used as the botanical for tea. It has been used for generations safely; at least, it is not associated with causing health problems. But, a history of safe use is not the same thing as safe. If laevo carvone is found in spearmint at 60% and it is used by itself as a food ingredient and all the other components of spearmint are also used as food ingredients in the same percentage as they are found in spearmint, are they safe? The answer is, probably. Or more accurately, there is a low risk that they are not safe. But is that enough? In today's world where we are able to measure to parts per billion as a matter of routine and there is a natural need for conclusive data, it is reasonable for someone to say, "Prove it." Even in 1959, the new FAA, largely believed by most well-informed individuals in both government and industry, to be overdue, there was a natural skepticism.

Back to our history lesson.

Food Additive Amendment of 1958

The FAA, or, The Food Additive Amendment of 1958 created the stunning requirement of premarket approval. The FAA made it the responsibility of Industry to prove that an ingredient was safe, rather than for the FDA to prove that the ingredient was not safe. For most flavor

ingredients, there certainly was enough information on the basis of which one could make an assumption of safety, but not enough information to serve as proof.

The immediate problem for the FDA was, of the thousand-plus substances added to food, which should be considered food additives and which should be considered GRAS. As you can image, there was an immediate backlog. The FDA quickly published a list of GRAS items, of natural products including spices, extracts and essential oils that totaled hundreds of products and included 27 specific synthetic chemicals. By 1960, it was clear the FDA was overwhelmed by the volume of work to be done based on the methodology that existed. It also became clear that the number of substances already being added to food in the form of flavors was so great, the small Flavor Industry was incapable of advancing the approval of products using the route of pre-market approval.

The Flavor Industry through the efforts of its primary trade association, The Flavor Extract Manufacturer's Association of the United States (FEMA) decided, in order to understand the magnitude of what was being required, to survey its members as part of a survey of all food ingredients being conducted by the National Academy of Sciences upon the request of FDA. This survey took place in 1959. The purpose was to identify what chemicals were used in flavors and in what amounts. The survey showed there were many more food ingredients, including flavors, in common use than the FDA anticipated.

According to one writer who was a key player from 1959 through the 1980s, the FDA was astounded to find that flavors accounted for 75% of all food ingredients.

The interesting thing about flavors that are added to foods is that they are mostly found in the food we eat as natural components because the flavorist typically seeks to mimic the natural flavor sensation of the foods that we're familiar with. Flavors added to foods are almost always found in minute quantities because they're naturally present in foods in such minute quantities – it only takes a tiny amount of a flavor for people to taste it. Because of their low dosage and consequently low exposure to humans, they are and were considered to be a low

safety risk. But, in 1960, while everyone, including the FDA, expected that flavor chemicals were low risk, expectation was not enough.

In 1959, within FEMA, there was a recently appointed Food Additives Committee chartered with the responsibility of getting the industry organized and making recommendations. The Chair of that Committee, Dr. Richard Hall, an employee of McCormick & Company, had the foresight to recommend the Flavor Industry hire as a consultant a scientist with a pedigree of academic achievements. His name was Ben Oser. Together, Ben Oser and Dick Hall analyzed the FAA and came to the conclusion that the only practical path open to the Flavor Industry was to use the GRAS exemption clause of the FAA. But to apply that GRAS clause, would require a cadre of scientists meeting the criteria to apply expert scientific training and experience. The foresight of Drs. Oser and Hall led to the birth of the FEMA Expert Panel.

The FAA held that GRAS status was accepted for an ingredient that met four criteria:

1. There must be general recognition of safety by qualified experts.
2. The experts must be qualified by training and experience to evaluate the substance's safety.
3. The experts must base their determination of safety on scientific procedures or on common use in food prior to 1958
4. The determination of general recognition for safety must take into account the conditions of intended use for the substance.

(Hallagan and Hall, 1995)

Flavor and Extract Manufacturers Association Independent Expert Panel

Faced with this challenge, the Flavor and Extract Manufacturers Association of the United States (FEMA) created an independent Expert Panel to determine the safety of the thousand-

plus flavor ingredients. As you have seen, the decision to create this panel was born of necessity.

The Panel was designed to be scientifically independent with up to 8 members who were experts in different scientific fields, including Molecular Toxicology, Metabolism and Bio Kinetics, Biochemistry, Organic Chemistry, Biotechnology, Pharmacology, Pathology, Microbiology, Medicinal Chemistry, and Toxicology. To say the least, the Panel was and is comprised by a group of recognized experts in areas of scientific disciplines related to the safety assessment flavor ingredients. Today, those fields include expertise in genotoxicity.

The FEMA Expert Panel was constituted based on the unique characteristics of flavors themselves. Flavors are often mixtures of individual chemicals and natural extracts that are mostly found in foods. The dosage in the flavors is typically at a low level and the use in the processed foods is often infinitesimal. Flavors can be complex mixtures of a hundred ingredients. When extrapolated into the finished processed food, the levels of specific ingredients can be in parts per million, or parts per billion.

Over the years, the process by which the Panel has evaluated flavor substances in order to determine whether or not to confer GRAS status has evolved. But the evolution has involved incorporating new branches of science that contribute knowledge. The basic framework has remained.

For all of the years of its existence, the Panel has met the criteria written in the FAA.

In order to be GRAS a substance must be generally recognized among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (…or experience based on common use in food) to be safe under conditions of intended use (21 U.S.C. Sec 321(s), 1988).

That is not a lot of words, but it is sets forth a big challenge.

To meet the requirements, the FEMA Expert Panel developed policies and operating requirements that would stand the highest degree of scrutiny.

There has never been any doubt that the members of the Expert Panel are and have always been well-regarded experts with academic pedigrees in precisely the scientific areas that pertain to the safety evaluation of flavor substances.

To support the need that their decisions are generally recognized, all the data the Panel uses in its evaluations has been made available so they can be reviewed by anyone. Initially the data was made available in the 1960s-1980s in the Scientific Literature Reviews published by the federal government's National Technical Information Service, and later in a series of peer-reviewed scientific journal articles.

To further support the notion of General Recognition, Expert Panel decisions to confer GRAS status must be unanimous.

In addition, all of the decisions are published so that they can be peer reviewed. In the case of the FEMA GRAS lists, the tradition has been to publish in the Journal of Food Technology. In addition to the many publications in the open literature, the full "FEMA GRAS list" is available to the public in the Flavor Ingredient Library on the FEMA website (www.femaflavor.org).

General recognition requires that information is available and that there is general agreement on the interpretation of the evidence. The definition of general is "extensive though not necessarily universal, most frequent but not without exceptions" (Hallagan and Hall, 1995; Hallagan and Hall, 2009).

Criteria for Determining GRAS Status

The Expert Panel uses five criteria for determining the GRAS status of a chemically defined substance, which is a single chemical:

1. Exposure – to the substance in specific foods, the total amount in the diet and the total poundage.
2. Natural occurrence in food
3. Chemical identity – including purity, method of preparation and specific chemical structure.
4. Metabolic and pharmacokinetic characteristics
5. Animal toxicity

(Woods, and Doull, 1991)

One of the jobs of the human body is to act like a waste disposal machine. Every substance we consume goes through complex chemical processes, the result of which is we gain nutrition, and excrete waste. Those processes that are understood by toxicologists, are observed by following the metabolic pathways of the chemical processes. "In general, metabolic pathways and toxicity are determined by the functional groups attached to a molecule. It is the functional groups that undergo successive transitions, as occur with hydroxyl, aldehyde and carboxyl groups in straight-chain aliphatic compounds, other compounds of similar basic structure are regarded as metabolized in the same way. On an aromatic ring, such groups act as "metabolic handles" which determine the direction of the biotransformation and detoxification. The toxicity of a compound in a homologous series can frequently be predicted from that of the adjacent members." (Oser and Hall, 1977)

One of the methods employed by the Expert Panel is to analyze a particular chemical within its class of structurally related compounds, an analytical technique long-recognized by the FDA as a very useful component of safety assessments. This analytical technique is evident in the Scientific Literature Reviews and the FEMA Expert Panel's many publications in which the

analytical paradigms are organized to facilitate analysis by groups of structurally related substances in which similar substances can be grouped together for consideration.

What all that means, in a nutshell, is that if you know the toxicology of geraniol, you can extrapolate that data to make accurate and informed judgements about the toxicity of geranyl acetate, geranyl butyrate, geranyl formate, geranyl propionate, which are all substances of a similar chemical structure. The knowledge of one chemical provides the useful knowledge for structurally related chemicals.

The panel then uses the "consumption ratio" analysis if appropriate and if data is available. The consumption ratio compares the quantity of a flavor ingredient consumed as a natural constituent of food with the quantity of the flavor ingredient consumed as an added flavor. It essentially asks—is this flavor consumed in greater amounts from its source? Or from its presence in packaged foods? (Stofberg and Krischman, 1985; Hallagan and Hall, 1995; Hallagan and Hall, 2009).

FEMA GRAS

Each GRAS publication includes a list of uses and their use levels to set the conditions of intended use for the substance. The custom has been for the Panel to provide usual and average maximum use levels with a note that states, "use level above the maximum may require reassessment by the panel."

The first FEMA GRAS list was published in 1965. It was called GRAS 3. The first FEMA GRAS number was number 2001 and was for Acacia Gum. Why GRAS 3 rather than GRAS 1 and why number 2001 rather than 0001? GRAS 3 was the first publication in which formal GRAS numbers were used. Prior to its publication, there had been two other publications that described FEMA's plans for GRAS assessments. The GRAS 3 publication constituted the original GRAS list of spices and natural products published by the FDA, as well as GRAS ingredients recently determined to be GRAS by the original FEMA Expert Panel. The reason why the first

FEMA number is number 2000 is that the National Academy of Sciences in its original survey of food ingredients in-use at the time of the 1958 FAA reserved 3000 numbers for flavor ingredients. Those numbers began with number 2001. It is interesting to note that today in 2019, we are getting closer to the FEMA GRAS number 5000, the last number reserved for flavor ingredients by the National Academy of Sciences. It will be interesting to see what happens when we surpass FEMA GRAS 5000.

GRAS 3 included those natural products such as lemon oil, lime oil, Licorice extract, lavender and orange oil that were found by survey to be in common use before 1958 where no issue of safety concern was determined.

For the next 40 years, literally thousands of substances were put through the high scrutiny FEMA Expert Panel process. The vast majority of those ingredients were single chemically-defined flavoring substances.

The FEMA GRAS process is subject to improvement as new advances in science are discovered and found to be relevant to safety evaluation. Over the decades, the Panel has conducted programs of affirmation and re-evaluation to employ new methods and to provide confidence about earlier judgments.

While the FEMA GRAS Program is a distinctly American endeavor, the science behind it is universal. One measure of this is to note that the Expert Panel—which began its history as a collection of distinguished American scientists—now counts among its membership a number of non-American distinguished scientists. Another measure is to consider other flavor safety evaluation programs. Not surprisingly, both the Joint FAO/WHO Expert Committee on Food Additives (JECFA) and the European Union- through the European Food Safety Authority- EFSA, have implemented assessment programs using principles consistent with those of FEMA GRAS assessment (Hallagan and Hall, 2009). In 1996, JECFA implemented a comprehensive safety assessment program for single chemically defined flavoring substances. The goal of the JECFA program is to create an open positive list of flavor ingredients that could be used by the Codex

Alimentarius Commission in the development of global food standards pursuant to the World Trade Organization Treaties (Hallagan and Hall, 2009).

There are almost 2800 FEMA GRAS substances. It is not hard to understand that it would be convenient for flavors approved for use in the United States to be manufactured with similar ingredients in Germany, Japan, China, Brazil, etc. The two mechanisms to make that happen are, for one, each country to recognize the approved ingredients of every other country, and second, that a global group of experts (JECFA) confirm approved status so that signatories to the WTO Treaties are comfortable confirming legal status for those ingredients. The second format is what is in place. This objective is the so-called "Global Positive List". This list is a destination, a goal. We are well on the way to its development, but we will never really get there. The important thing is to keep moving forward with the development and acceptance of a globally harmonized approach to flavor safety evaluation.

It is a reasonable question to ask how well the FEMA GRAS program has performed. The clearest indicator of the success of the program is the endorsement of the FEMA GRAS program by the FDA.

In 1997, the FDA codified its voluntary GRAS notification program. While there have been many food ingredients that have been made GRAS using this route, particularly by giant companies with virtually unlimited resources that are able to assemble their own Panel at their own expense. The Flavor Industry, which has many small and medium-sized family-owned companies, has used the route provided by the FEMA GRAS Panel to introduce novel new ingredients.

Over the decades, FEMA has tackled some complicated issues for which significant investment was necessary by the Flavor Industry as a whole. Perhaps the most notable of these issues was for processed flavors. Processed flavors are manufactured by heating a mixture of carbohydrates and proteins in the form of amino acids. The potential combinations are virtually endless. For the most part, these processed flavors produce savory flavors that can be

added to soups, gravies, etc. These are the so-called Maillard Reaction products. An example of this is the sautéing of mushrooms. Take cold mushrooms with almost no aroma and put them in a skillet and cook them. Before long, a wonderful aroma is produced. The same thing happens with onions.

The safety issue of concern was that there is the possibility that under certain conditions, polycyclic heteroaromatic amines (PHAs), which occur in cooked meats, particularly grilled meats, may be formed during the process of manufacturing a Process Flavor. To resolve this issue of concern, FEMA, in consultation with the FDA, conducted an extensive study to determine the degree to which PHAs were formed. After years of study, it was concluded that the potential intake of PHAs from processed foods containing Process Flavors, was negligible compared to the intake of PHAs from cooked foods and that Processed Flavors did not represent a safety hazard "under conditions of intended use" (Hallagan, 2005). Of course, FEMA provided all of the data to the FDA.

Over the past two decades, FEMA has addressed a variety of safety assessment issues, such as the role of intake assessments and genotoxicity data in flavor safety evaluations when such issues have been identified by national, regional and global safety assessment groups. For example, as was the case right after the passing of the FAA, the U.S. Flavor Industry has conducted periodic surveys of the industry aimed at determining if the poundage of flavor ingredients has changed so substantially so as to change the estimated human exposure upon which safety calculations are made. This is a massive project and takes place every 5 years. This technique has been so helpful that there is now a Global effort to survey the global industry to provide the same data. Once again, the world is adopting the United States approach.

Use levels in specific food categories are not meant to be rigid within the context of GRAS. What has become standard practice is that as new applications for standard products are found, and significant increases in use levels are then brought to the attention of the Panel so

they can be re-evaluated based on the new use level. Put succinctly, “it is the use of a substance, rather than the substance itself, that is eligible for the GRAS exemption.”

You may remember at the beginning of this discussion that I mentioned the first GRAS list included natural products such as essential oils and spice extracts. Those were included on GRAS 3 primarily because they had a long history of use prior to 1958 (in some cases, many hundreds of years,) without apparent safety concerns.

For all the years from 1965 until 2004, most of the thousands of flavor ingredients added to the FEMA GRAS list were individual chemically-defined substances. In 2004 and 2005 papers were published in *Toxicology Letters* and *Food and Chemical Toxicology* that described a new, state-of-the-art methodology by which natural products such as essential oils, oleoresins and botanical extracts could be evaluated by the FEMA Expert Panel for inclusion on the FEMA GRAS list. These papers define Natural Flavor Complexes as mixtures of chemicals obtained by applying physical separation methods to botanical sources such a pulp, bark, peel, leaf, bud, berry and flower of fruits, vegetables, spices and other plants.

Natural Flavor Complexes are comprised mostly of terpene hydrocarbons, esters, aldehydes, alcohols, acids and ketones that are produced by well understood and documented biosynthetic pathways in plants.

As you can imagine, since the vast majority of the FEMA GRAS list mimics the constituents of natural sources, the vast majority of natural products are comprised of chemicals that are already FEMA GRAS. Take a simple essential oil like orange or lemon. You can find the gas chromatograph (GC) curve for lemon oil on slide 27 of the PowerPoint. If you look at the labeled peaks you will see that each of them has a GRAS number in parentheses next to the description. If a new Natural Flavoring Complex is comprised of 30 components and each of those components is already GRAS, it stands to reason that the Natural Flavoring Complex would be GRAS. That is one aspect of what is called The Naturals Paradigm in the article, Smith et al 2004.

The Naturals Paradigm

The Naturals Paradigm creates a decision tree for analyzing the safety of a natural product whereby all known components are grouped by levels of safety concern and evaluated.

While you might think this would be easy, it is not. This is because, many natural products contain not only volatile components, but also a meaningful percentage of non-volatile components, such as triacyl glycerides, colors, peptides, many of which are either difficult or impossible to identify.

The Naturals Paradigm focuses on the constituents or congeneric groups of constituents, which because of structure or concentration might pose a health concern, and then evaluates the safety of these known and unknown components by applying the most pessimistic assumptions for the unknown components. If a relevant safety concern arises from a branch of the decision tree, the substance can be rejected based on the need for additional data. If the decision tree process does not reveal any reasons for concern, the product is deemed GRAS.

Over the past 10 years a number of essential oils, including very small volume and large volume products, have been determined to meet the criteria for FEMA GRAS status. The Expert Panel continues to modify its approach to safety evaluation as advances in science occur. In fact, just a few weeks ago a modification to the Naturals Paradigm was published in the Journal of Food and Chemical Toxicology (Cohen et al., 2018). This updated paradigm is also currently being used to ensure that the GRAS status of all of the FEMA GRAS listed essential oils, extracts and others remain current via an ongoing reevaluation program.

Natural and Synthetic

Let's discuss natural and synthetic flavors. But first, let me set the stage. It is fair to say, in the natural foods consumed every day that form our diet, there are literally thousands of

chemicals, many of which, in large doses, could be considered toxic. That fact does not imply that there is a hazard or risk. The level of the chemical exposure present in consuming regular, healthy foods, is so low that the exposure is fine.

In the case of the word "natural," it probably does not surprise you that there is an official definition in U.S. law. What might surprise you is that there is no regulatory definition of what is a "natural" food, but that there is only a definition of what is a "natural" flavor. The primary definition of natural flavor is in the FDA's regulation at 21 CFR 101.22(a) (3). In fact all food and food ingredient regulations by the FDA can be found in the Code of Federal Regulations (CFR) under Part 21. The FDA has stated only a policy, not a regulation, to define what a "natural" food is.

For the purpose of this seminar, I do not want to dwell on the preference by U.S. consumers to purchase natural foods that contain natural flavors, I want to address the safety of natural and artificial ingredients.

The best way I can think of to make a comparison is by focusing on the same chemical substance derived by different routes. I have chosen citral, the primary flavor constituent of litsea cubeba oil and the principle characterizing constituent of lemon oil.

Lemon oil is one of many citrus essential oils that is produced by a process known as expression otherwise known as cold pressing. Unlike spearmint, where the essential oil is extracted by steam distillation, lemon oil is extracted using a physical process that mimics squeezing the peel of a lemon to release the oil. The process of mechanical expression can be observed on slides 33-35 in the PowerPoint. If you were to smell lemon oil cold pressed, you would find that it smells like lemon. If you were to next smell citral, you would also find that is smells lemony. Now, take a look at the GC curve of lemon oil on slide 27 of the PowerPoint. Citral is actually two isomers, one is called neral and the other geranial. Together, they are citral. You may be surprised to learn that the best quality lemon oil only contains 3% total citral.

Let's take a look at another oil that contains citral, called litsea cubeba oil. As you can see from the GC curve on slide 29 of the PowerPoint, the citral content is 75%. We can extract the citral from litsea cubeba oil using fractional distillation. You can see a picture of fractional distillation equipment on slide 45 of the PowerPoint. The litsea cubeba oil is loaded in the still pot, a vacuum is applied, and the oil is heated to the point where it becomes volatile. It travels up the column, which contains packing material, such as stainless mesh or stainless steel springs or some other partial obstacle that makes it possible to separate the citral in the Litsea from the other components.

Distillation is a process that has been around for centuries. So citral can be isolated from litsea cubeba oil using a physical process that meets the definition of natural. Citral from litsea is natural. However, citral can also be manufactured from turpentine by complex multi reaction chemistry that employs chemical catalysts. For that matter, it can also be made from other starting materials. The question I want to get around to answering is, "Is all food grade citral, regardless of the process and starting material, safe under conditions of intended use?"

It might interest you to learn that in Japan there is no legal distinction in consumer product labeling between a consumer product that is flavored with natural ingredients and one flavored with synthetic ingredients. The label simply indicates, "flavored".

In the United States, going back to the 1970s and 1980s the concept of natural was promoted by food companies using marketing techniques to capitalize on consumer preferences for food products formulated with natural ingredients, including natural flavors.

Saying that a food is flavored with a natural flavor is emotionally satisfying to consumers who conjure up pictures of farms and plants. While saying that something is artificially flavored can conjure pictures of stainless steel reaction vessels and large factories. One is a happy thought and the other could be scary. But science is about truth, and the truth is that the human body does not make a distinction between the origin or method of manufacture of a chemical substance that it metabolizes.

From a safety perspective, natural citral and synthetic citral are both GRAS. They are equally safe under their conditions of intended use. That is because the human body metabolizes natural citral the same way as it metabolizes synthetic citral.

In the United States, flavors must be formulated with GRAS substances or with ingredients considered as food additives. You can find a formula for a simple raspberry on slide 38 of the PowerPoint. All of the chemicals listed are GRAS. Many of them are found in a raspberry. Here is the same formula written two ways. On the left, we have included natural versions for some of the chemicals and on the right, synthetic versions. As you can see, the formula is the same.

Now let's consider the issue of safety, which, after all, is the subject of this lecture. In both formulas, the chemical ingredients are the same. Only the origins are different. On the right, the chemistry has been done in factories. On the left, the chemistry has been done inside botanicals from which the products have been isolated, reacted or fermented. From a safety perspective, Food Law in the United States supports the conclusion that both are safe based on their intended use.

For those of you in the audience who are not scientists, I wonder if this conclusion is not satisfying. But, Food Scientists know that today's food products are developed based on their safety, nutritive value, taste, convenience and affordability. A major job for any food product developer is to develop products that maximize the attributes of total quality and affordability when developing a new food product. I find it satisfying to know that the added flavors, whether natural or synthetic, are proven to be safe. It makes me proud to work in an industry that is passionately committed to consumer safety.

Food Scientists understand the many food products need to be highly processed to insure that the final product does not quickly spoil or permit dangerous microorganisms to grow. Food Scientists are also aware that, in the development of safe foods, high thermal treatments that ensure safety, often destroy the natural flavors, pigments, nutrients and in some cases, the

texture of food. For that reason, Food Scientists are confronted with the challenge to develop food products that can survive normal processes and for that reason they add flavors, which are safe and are GRAS (under conditions of intended use). Vitamins are also added to restore their content to the original level found in food. It is interesting that the vitamins that are added are produced synthetically, yet, they are not held to the same regulations as flavor ingredients, which require that they should be labeled as artificial. There are many reasons to use food ingredients including flavors, vitamins, and colors, in modern food products, whether derived naturally or synthetically. As the population grows and as the world's population becomes wealthier, there is going to be an increase in the demand for processed affordable food. There may very well not be enough natural materials and there will be increased demands placed on food companies and food developers to provide safe, nutritious, good-tasting, affordable food.

Conclusions

Some of you may still believe something just seems wrong. I can tell you right now that I have friends, well-educated friends, who I am absolutely certain avoid purchasing processed foods that are flavored with artificial flavors. They probably have no understanding that flavors formulated with GRAS ingredients are safe whether the ingredients are natural or synthetic.

We could spend another hour talking about something known a Chemophobia – the fear of chemicals.

But you are all scientists in training. I can tell you that anyone who argues with the notion that eating healthy foods produced on local farms is not to be believed. Fresh local foods like grains and vegetables and poultry and meats and tree nuts, are what humans eat. But, while that is absolutely true, it is also true that flavors in processed foods are safe under their conditions of intended use.

You all represent the next generation of scientists. Perhaps one or two of you will become toxicologists. But together, I am pretty certain you are well-respected by your peers for your academic achievements. Earning a degree in Engineering, Chemistry, Biology and Food Science is not easy. Your peers know you are smart.

As you interact with your peers, consider sharing your opinions with them on the issue of chemicals. We, in this room, know that we are made up of chemicals. Our foods, all of them are made up of chemicals. Chemicals are simply substances and building blocks. They do not need to be scary.

And one last point, the Flavor Industry is fascinating. If you find that this talk has piqued your interest, consider learning more about flavors. It is a wonderful industry in which individuals with many different skills make a good living working in a field with plenty of innovation.

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