J Am Oil Chem Soc (2020)
DOI 10.1002/aocs.12366

REVIEW

Regulatory Changes Affecting the Production and Use of Fats and Oils: Focus on Partially Hydrogenated Oils

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Received: 21 August 2019 / Revised: 25 March 2020 / Accepted: 26 March 2020

Abstract Partially hydrogenated oils (PHO), the products of incomplete catalytic hydrogenation of food oils, have been widely employed by the food industry for more than a century. Their exceptional stability and technologic characteristics made them the preferred choice for the production of several food products including margarines, bakery goods, and frying oils. Some of these highly prized characteristics were provided by the high content in *trans* fatty acids (TFA), defined as fatty acids with one or more isolated double bond in trans configuration. The discovery of negative health effects associated with dietary intake of TFA triggered world-wide a wave of regulatory actions aimed to curb their consumption. PHO became the main target of most campaigns aimed to reduce consumption of TFA, and their fortune in the food industry progressively faded. At the 2017, AOCS Annual Meeting in Orlando, a group of experts from regulatory agencies and industry from North America and Europe met to discuss the current status of government regulations and industry adaptations regarding the productions and use of PHO. The discussion was enriched by including the impact on fats and oils production of the 2016 amendment of the Toxic Substances Control Act of 1976 (TSCA). The present publication may not include all regulatory changes that took place after this symposium, in 2017.

Keywords Partially hydrogenated oils · PHO · Trans fat

J Am Oil Chem Soc (2020).

Abbreviations

AFSSA	agence française de sécurité sanitaire des aliments
BHA	butylated hydroxyanisole
BHT	butylated hydroxytoluene
CAS	chemical abstracts service
CASRN	chemical abstracts service registry number
CBI	confidential business information
CHD	coronary heart disease
CLA	conjugated linoleic acid
CVD	cardiovascular disease
DGAC	dietary guidelines for Americans
DHA	docosahexaenoic
EC	European Commission
EFSA	European Food Safety Authority
EPA	U.S. Environmental Protection Agency
EPA	eicosapentaenoic acid
FAME	fatty acid methyl esters
FAO	Food and Agriculture Organization
FSANZ	Food Standards Australia New Zealand
GE	glycidyl esters
GMO	Genetically Modified Organisms

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GRAS	generally recognized as safe
HDL	high-density lipoproteins
HDL-C	high-density lipoprotein cholesterol
HOCAN	high oleic canola
HOSOY	high oleic soybean
HOSUN	high oleic sunflower
IFIC	International Food Information Council
iTFA	industrial TFA
LDL	low-density lipoproteins
LDL-C	low-density lipoprotein cholesterol
LEAR	low erucic acid rapeseed
MCAN	Microbial Commercial Activity Notice
MCPD	3-monochloropropane-1,2-diol or 3-chloropropane-1,2-diol; 2-monochloropropane diol
MUFA	mono-unsaturated fatty acids
NGO	nongovernment organizations
NOC	Notice of Commencement
nTFA	natural TFA
OSI	oxidative stability index
PBT	persistent, bioaccumulative, and toxic
PHO	partially hydrogenated oils
PMN	premanufacture notification
PUFA	polyunsaturated fatty acids
SBA	small business administration
SDA	Soap and Detergent Association
SFA	saturated fatty acids
SNU	significant new use
SNUR	significant new use rule
TBHQ	tertiary butylhydroxyquinone
TFA	*trans* fatty acids
TSCA	Toxic Substances Control Act
US FDA	United States Food and Drug Administration
USP	United States Pharmacopeia
UVCB	unknown or variable composition, complex reaction products, or of biological materials
WHO	World Health Organization

The Rise and Fall of Partially Hydrogenated Oils in Food Supply Chain

Pierluigi Delmonte, Sneh Bhandari

Partially hydrogenated oils are defined as oils that have been subjected to the procedure of hydrogenation, without reaching the complete elimination of unsaturations. The final iodine value, a measure of the residual unsaturation, must be greater than 4 (US FDA, 2015); otherwise, the oil or fat is defined as fully hydrogenated (USP, 2018). While this difference is now widely accepted, no clear distinction was made in the early PHO era probably due to the lack of its requirement as well as analytical capabilities necessary for this characterization.

The rise in margarine popularity during the last century, driven by the necessity for cheap and stable solid fats, could not be achieved without the invention of hydrogenated oils. Oleomargarine (later shortened to "Margarine") was invented and patented in 1869 by Hippolyte Mège-Mouriès per request of Emperor Napoleon III, in need of a cheap butter alternative to feed the French armed forces and the working class (Rupp, 2014; Wolfe et al., 2000). The original formulation was made of beef fat (tallow) and skimmed milk, and was initially produced in 1871 by the Dutch company Jurgens now part of Unilever (Unilever, 2009; Rupp, 2014). Almost 3 decades later, Sabatier and Senderens discovered the process of hydrogenation (Sabatier and Senderens, 1899), by passing vapor of unsaturated organic molecules mixed with hydrogen over hot, finely divided nickel. A few years later in 1902 Wilhelm Normann patented in Germany (Leprince and Siveke, 1902; Patterson, 1998), and Britain (Normann, 1903) the hydrogenation of oils, starting a new era in the production of fats and oils. Based on this revolutionary discovery, in 1909, Joseph Crosfield & Sons started the first large-scale production of hardened fat, and by 1914 Jurgens built world-wide more than 20 industrial hydrogenation plants (Knothe, 2004). Meanwhile, in the US, Procter & Gamble developed an industrial process to transform liquid cottonseed oil into a solid fat and in 1911 it began the production of the first hydrogenated shortening, Crisco, primarily composed of partially hydrogenated cottonseed oil (Schisgall, 1981).

The economic depression of the 1930s and the limited availability of animal fats during World War II, combined with relevant advances in the manufacturing of hydrogenated oils, led to the progressive replacement of animal fats in margarines with hardened vegetable oils. In 1945, oleomargarine produced according to the original patent almost completely disappeared from the US market (Clark, 1986). The large availability of cheap cottonseed and soybean oil catalyzed this transformation, and margarines produced by lower cost progressively replaced butterfat and other animal fats (Shurtleff and Aoyagi, 2005).

The optimization of the hydrogenation process allowed the creation of novel, highly tailored functional edible fats to be used for shortenings, confectionery, baking, and other applications. The precise content of TFA, a byproduct of the hydrogenation process, gained a central role to achieve the technologic properties necessary for the development of these products. The adjustment of the hydrogenation reaction parameters such as the nature and concentration of catalyst, hydrogen pressure, temperature, and agitation, provided the desired formation of trans double bonds (Ackman and Mag, 1998). The TFA content of these PHO was commonly around 25 g per 100 g and ranged from 10 to 60 g per 100 g (Tarrago-Trani et al., 2006). These

malleable fats were solid at room temperature but melted at a specific desired temperature, depending in part on their TFA concentration. An oil could be converted from a liquid into a semisolid, plastic fat, closely resembling butter or lard in texture, and thus suitable for use as a substitute of butter or lard at a lower cost. Also, unlike butter, PHO could be taken out of the refrigerator and immediately spread on bread, a feature achieved by controlled hydrogenation to give the desired texture (Clark, 2003). Partial hydrogenation was also used to achieve unique oil/fat functionalities including flavor stability and retention, reduced oxidative rancidity, and off-flavors production in frying applications. The reduction of the iodine value of oils and fats used for manufacturing margarines by partial hydrogenation also improved the product shelf life and decreased the need for refrigeration (Weber and Alsberg, 1934).

The producers of traditional animal fats challenged the expansion of the margarine industry and several US states introduced laws that restricted the sale of margarine. Some states permitted the sale of margarine but not with yellow coloration, while others required margarine to be dyed to unappealing colors as pink. The last legislation regarding the coloration of margarines was repealed by Wisconsin in 1967. But the margarine industry thrived against all odds. In 1965, the US per capita consumption of margarine surpassed that of butter and more than doubled it 10 years later, a dominance which has been sustained into the last years of the twentieth century (Vaisey-Genser, 2003).

In the mid 1900's, research began to investigate the connection between diet and long-term health. Nutritional implications played first a positive and then negative role in the popularity of PHO. Concerns regarding the impact on health of animal fats rich in saturated fatty acids (SFA) and cholesterol provided a boost in the sale of PHO, which were proposed as healthier alternative (Formo, 1979). *Trans* fatty acids were not distinguished from other unsaturated fatty acids. The remarkable popularity of PHO resulted in deeper scrutiny on their impact on human health and researchers started suspecting their role in heart diseases (Enig, 1978; Thomas et al., 1981). In 1990 Mensink and Katan showed that TFA consumption causes an increase in low-density lipoprotein cholesterol (LDL-C) and a decrease in high-density lipoprotein cholesterol (HDL─C) in blood, leading to higher risk of heart disease (Mensink and Katan, 1990). The follow-up study 2 years later using lower amount of TFA, confirmed these results and also showed a linear dose effect of TFA on raising LDL-C and lowering HDL-C levels in blood (Zock and Katan, 1992). An observational study performed on 85,095 women at the same period strongly supported the theory that intake of partially hydrogenated vegetable oils contributed to the risk of having a heart attack (Willett et al., 1993). The response of regulators to these findings and other related reports is described below in the appropriate sections of this review. As a consequence, the food industry removed PHO from most products by modifying their formulations, using oils with modified composition, applying other technologies such as complete' hydrogenation and interesterification (Napolitano and Giuffrida, 2009).

Meanwhile, in the US another emerging factor may affect the production of PHO and its substituents: the Toxic Substances Control Act (TSCA), the federal law that regulates industrial chemical substances used in applications *other* than food, drugs, cosmetics, and pesticides, or other uses that are regulated by other federal authorities. TSCA was significantly amended in 2016, and these new regulations may affect the production of fats and oils.

A Hot Topic symposium was organized at 2017 AOCS Annual Meeting in Orlando to discuss the various regulatory changes worldwide related to food sources of TFA and the impact of these changes on the food industry. This review is a compilation of the topics discussed at the symposium. The opinions expressed by individual authors and institutions may not necessarily reflect the views of all contributors.

A US Regulatory Review: Partially Hydrogenated Oils and Trans Fat

Mical Honigfort, PhD

Trans fats are formed during the hydrogenation of oils and also occur naturally in meat and dairy products. Oils that are partially hydrogenated contain the highest amount of trans fats; these oils typically contain from 25% to 40% trans fat. Trace amounts of trans fat are also found in non-hydrogenated refined oils resulting from processing and in fully hydrogenated oils because of incomplete hydrogenation. Partially hydrogenated oils historically have been the primary source of industrially produced trans fats and have been in the food supply since their commercialization in the 1940s. Because of their technical properties such as improving shelf-life and stability in products, PHO have been used to make foods such as margarine, shortening, and baked goods.

In the U.S., a substance added to food is a food additive unless it meets one of the exceptions under the Federal Food, Drug, and Cosmetic Act. The term "food additive" is defined by law, and all food additives require pre-market approval by FDA through a process whereby FDA reviews the relevant scientific data and makes a determination as to whether the additive is safe under the intended conditions of use. For food additives that are not food contact substances, any person may submit a food additive petition seeking approval for its use with the supporting safety information. A successful petition will result in an

amendment of the food additive regulations authorizing its use. A food additive regulation prescribes the identity and use of the additive as well as any limitations and specifications. Substances that are generally recognized as safe (GRAS) either based on substantial history of consumption prior to 1958 or by general recognition of safety by qualified experts are excepted from the definition of "food additive." Regardless of whether a substance is legally considered a food additive or a GRAS substance, it must meet FDA's safety standard of "reasonable certainty of no harm" under its intended conditions of use. Commonly used PHO such as partially hydrogenated soybean oil and partially hydrogenated cottonseed oil had long been considered GRAS based on their history of use in food. FDA also affirmed two specific PHO as GRAS, partially hydrogenated low erucic acid rapeseed (LEAR/canola) oil (1985) and partially hydrogenated menhaden oil (1989). These oils are listed in FDA's GRAS regulations, but neither is extensively used by the food industry.

In the 1990s, FDA reviewed the available scientific evidence concerning the adverse effects of trans fat consumption on blood cholesterol and increased risk of coronary heart disease. To assist consumers in making healthy dietary choices, FDA proposed to amend its regulations to require declaration of trans fat content on the nutrition facts label of foods (US FDA, 1999). The objective of this proposed action was to help consumers determine how each food product contributes to their overall dietary intake of trans fat. In 2003, FDA issued a final rule (US FDA, 2003) amending the nutrition labeling regulations to require declaration of the trans fat content of food on the label of conventional foods and dietary supplements. This rule, which became effective on January 1, 2006, required the declaration of trans fat on the nutrition facts label if the food contained 0.5 g trans fat or more per serving. For foods with less than 0.5 g of trans fat per serving, the rule permitted food labels to declare the trans fat content as 0 g per serving due to analytical limitations. Many food manufacturers voluntarily reformulated products to reduce or eliminate partially hydrogenated oils because of this action by FDA.

In 2005, the Institute of Medicine recommended that trans fat consumption be limited as much as possible while maintaining a nutritionally adequate diet, recognizing that trans fat occurs naturally in meat and dairy products. After trans fat labeling became mandatory, FDA remained committed to trans fat reduction due to the increasing body of scientific evidence demonstrating the adverse effects of trans fat on human health. Trans fat reduction was part of the agency's 2012–2015 Foods and Veterinary Medicine Strategic Plan and was part of the Department of Health and Human Services' Million Hearts Initiative. FDA also received two citizen petitions (in 2004 and 2009) requesting that the agency revoke the authorizations for PHO.

In 2010, to determine the status of trans fat consumption in the U.S., FDA conducted a study to assess dietary intake of trans fat (Doell et al., 2012). FDA scientists found that as a result of voluntary reformulations prompted by the labeling requirement, consumption of trans fat from PHO had decreased significantly. In 2003, FDA estimated that the intake of trans fat from PHO by the adult population was 4.6 g per person per day for adults. By 2010, this had decreased to a mean intake of 1.3 g per person per day. However, if a consumer consistently chose the products with the highest levels of trans fat from PHO, they could consume double that amount, 2.1 g per day. Intake of trans fat from natural (ruminant) sources was estimated to be 1.2 g per person per day in 2002 and has remained relatively unchanged. In 2010, the major contributors to trans fat intake from PHO in the U.S. were savory snacks (primarily microwave popcorn), frozen pizza, cakes, cookies, margarines/spreads, coffee creamers, and pies.

In 2013, based on new scientific evidence and findings of expert panels, FDA issued a notice in the *Federal Register* with its tentative determination that there is no longer a consensus that PHO can be considered GRAS (US FDA, 2013) and therefore are food additives subject to the premarket approval provisions in the Federal Food, Drug, and Cosmetic Act. The process for FDA to issue such a notice regarding the GRAS status of a food ingredient is set forth in the regulations in title 21 of the Code of Federal Regulations, section 170.38. As part of this process, FDA gave interested parties 120 days to comment (a 60-day initial comment period followed by a 60-day extension). The agency stated that the fact that a substance was commonly used in food prior to 1958 is not sufficient to support continued GRAS status if there is no longer a scientific consensus that the substance is safe for the intended use in food.

The tentative determination summarized the health risks associated with the consumption of trans fat, opinions of expert panels, as well as the Institute of Medicine's, 2005 recommendation to limit trans fat consumption as much as possible. In making its tentative determination, FDA considered information from controlled feeding trials, which demonstrated cause and effect relationships of trans fat intake on LDL-C and HDL-C concentrations, as well as data from prospective observational studies, which showed the association of trans fat intake with coronary heart disease outcomes. The consistent results from both types of studies strengthened the scientific evidence of the adverse effects of trans fat. Expert panels also affirmed this evidence and recognized the progressive and dose linear cause and effect relationship between trans fat intake and risk factors for coronary heart disease. FDA also noted that studies had connected trans fat consumption to other adverse effects on health, such as insulin resistance and diabetes risk. In the notice, FDA stated that removal of PHO from

the food supply could prevent coronary heart disease events and deaths.

In 2015, after reviewing more than 6000 comments received in response to the tentative determination, FDA concluded that there was a lack of convincing evidence that PHO are GRAS for use in human food and issued its final determination as a declaratory order in the *Federal Register* (US FDA, 2015). In the order, FDA defined PHO based on iodine value to differentiate them from fully hydrogenated oils (fully hydrogenated oils are excluded from FDA's 2015 order), indicated that interested parties may submit food additive petitions to FDA for uses of PHO for which they can demonstrate safety, and established a compliance date of June 18, 2018. Since the symposium, in May 2018, FDA published a Federal Register notice extending the compliance date for certain uses of PHOs (US FDA, 2018).

Current and Proposed Canadian Regulations Regarding Partially Hydrogenated Oils and Trans Fat

Dr. William Yan

Trans fats are a type of unsaturated fatty acid (Institute of Medicine, 2005). They are found naturally at relatively low levels (between 0.5% and 8% of the total fat content) in dairy products and ruminant meats (for example, beef, lamb) and they can also be industrially produced (Mendis et al., 2008; Ratnayake and Zehaluk, 2005). The major source of industrially produced trans fats are PHO, which are produced as a result of a process called partial hydrogenation. PHO are used to make products such as shortenings and margarines and for processing, baking, and frying. Generally, products made with PHO have a longer shelf life than if made with liquid oils, and are more stable and break down less easily under conditions of high-temperature heating (Khor and Esa, 2008).

The consumption of trans fats increases the risk of coronary heart disease (CHD) (Oh et al., 2005; Oomen et al., 2001), one of the leading causes of death in Canada (Statistics Canada, 2015). Current hypothesis on the mechanism through which trans fats increase CHD risk is by altering blood lipid levels. Trans fats raise levels of LDL-C (the "bad" cholesterol), lower levels of HDL-C (the "good" cholesterol) (Brouwer, 2016). The negative effects of trans fats on blood lipids have a continuous dose–response relationship (Brouwer, 2016) meaning any incremental increase in trans fat intake increases CHD risk (Institute of Medicine, 2005).

In the 1990s, Canadians had one of the highest average intakes of trans fat in the world (3.7% of total calories) (Chen et al., 1995; Ratnayake and Chen, 1995). Since the early 2000s, Health Canada has pursued a multi-faceted approach aimed at reducing the trans fat intakes of Canadians. This led Canada to be the first country to mandate the declaration of trans fat in the Nutrition Facts table (2002). At the same time, regulatory criteria were established to allow nutrient content claims such as "trans fat free" to be listed on product labels to encourage reformulation and to help guide consumers toward healthier alternatives.

In 2005, a multi-stakeholder Trans Fat Task Force was established by Health Canada with a mandate to develop recommendations and strategies to reduce industrial trans fats in Canadian foods to the lowest level possible. In 2006, the Task Force published a final report in which it was recommended that a regulatory approach be taken to limit levels of trans fats in the food supply to 2% of total fat content for vegetable oils and soft spreadable margarines and 5% of total fat content for all other foods (The Trans Fat Task Force, 2006). The following year, Health Canada adopted the recommendations of the Task Force with respect to the trans fat limits in foods and also introduced the Trans Fat Monitoring Program. At that time, the then Minister of Health called on the food industry to achieve these limits within 2 years under a voluntary approach. Between 2007 and 2009, four sets of Trans Fat Monitoring Program data were posted on the Health Canada website revealing industry's progress toward meeting the voluntary targets.

Data published over the last decade suggest that initiatives to decrease the trans fat consumption of Canadians have been highly effective. A risk assessment by Health Canada estimated that by 2007 the average trans fat intake for all Canadians (age 1 year and older) had decreased to 1.42% of total energy (Ratnayake et al., 2009). Furthermore, findings of the Trans Fat Monitoring Program showed that by 2009 approximately 75% of prepackaged foods and nearly all restaurant foods monitored were meeting the voluntary targets. Lastly, a 2011 survey of approximately 10,000 prepackaged and restaurant foods on the Canadian market found that 97% of foods surveyed met the voluntary targets for trans fats (Arcand et al., 2014).

Despite the multiple measures described above, as of 2011, there continued to be certain food categories that had large proportions of foods not meeting the trans fat targets. These categories included: frostings, coffee whiteners, shortbread cookies, dairy-free cheeses, lard, and shortening (Arcand et al., 2014). Additionally, a 2011 risk assessment by Health Canada showed that some subpopulations were still at risk for higher trans fat intakes, including children and teens, Canadians living in remote areas, price sensitive consumers, and those who regularly consumed foods remaining high in trans fats (Krenosky et al., 2012). Therefore, more needed to be done in order to further reduce trans fats in the Canadian food supply.

In the 2015 Mandate Letter from the Prime Minister of Canada, the Minister of Health committed to bringing in tougher regulations to eliminate industrially produced trans fats (Office of the Prime Minister, 2015). In response to this commitment, in May 2016, Health Canada launched a Call for Data to collect information on the current use of PHO in the food supply (Health Canada, 2016a). Although the response rate was low, many industry representatives indicated that their companies were moving away from PHO use. Importantly, none of the data received supported the need to maintain allowance for PHO use.

On October 24, 2016, the Minister of Health announced a multi-year Healthy Eating Strategy as part of the Government's vision for a healthy Canada. One of the intended outcomes of this Strategy is to help make the healthier food choice the easier choice. The Healthy Eating Strategy involves actions on a number of initiatives including the elimination of industrially produced trans fats in foods (Health Canada, 2016b).

In order to achieve the public health objective of reducing the trans fat intakes of the great majority of Canadians to less than 1% of total energy, Health Canada proposed to prohibit the use of PHO in foods sold in Canada (Health Canada, 2017). After two rounds of consultation in 2016 and 2017, Health Canada's ban on PHO came into effect on September 17, 2018 (Health Canada, 2016c, 2017). It is now illegal for manufacturers to add PHO to foods sold in Canada. This includes both Canadian and imported foods, as well as those prepared in all food service establishments. The prohibition excludes fully hydrogenated fats and oils. The ban came into effect with the addition of PHO to Part 1 of Health Canada's *List of Contaminants and Other Adulterating Substances in Foods* (Health Canada, 2018). Although the United States and Canada used different mechanisms to address PHO use in foods: through classification of PHO as an adulterating substance in Canada and by removing the GRAS status for PHO in the USA, they will ultimately achieve the same public health objective of eliminating PHO from the food supply."

Trans Fatty Acids in Foods: Lessons Learned and the Way Forward

Fabiola Dionisi, Mathilde Fleith

Definition and Occurrence of *Trans* Fatty Acids

Trans fatty acids are unsaturated fatty acids with at least one nonconjugated carbon–carbon double bond in the trans configuration. They can be divided according to their source in naturally occurring TFA and industrial TFA. Natural TFA (nTFA) are formed in the gut of ruminant animals by bacterial partial biohydrogenation of unsaturated fatty acids. Industrial TFA (iTFA) are formed mainly during the process of partial hydrogenation of oils. The difference in the chemical and enzymatic hydrogenation mechanisms for unsaturated FA results in differences between nTFA and iTFA. Indeed, both nTFA and iTFA are a mixture of different isomers in different relative percentages: vaccenic acid (trans 11-18:1) is generally the most abundant isomer in nTFA while elaidic acid (trans 9-18:1) is the predominant isomer in iTFA.

In the human diet, milk and derivatives (cheese, butter …) as well as different types of meat are the principal sources of nTFA, while PHO are the principal sources of iTFA. Milk fat typically contains 2–5 g nTFA per 100 g (Aro et al., 1998). On the other hand, PHO may contain up to 60% of iTFA.

Intake of *Trans* Fatty Acids

FAO/WHO recommends an intake of total TFA not higher than 1% of the total daily energy of the diet (FAO/WHO, 2010). During the past 20 years, intakes of TFA have dramatically reduced and, currently, the average total TFA consumption in the majority of countries for which data are available is below the limit of 1% of energy (Wanders et al., 2017). Some countries (*e.g.*, Egypt, with an intake of 6.5% energy) still consume excessive amounts of TFA (Micha et al., 2014). Also, even though the average population intake might be low, there are still individuals and subgroups with high TFA intake in many populations (Stender et al., 2008). Recent data on intakes of nTFA and iTFA exist for several countries, *e.g.*, Japan, Indonesia, France, Spain, Australia and New Zealand (AFSSA, 2009; FSANZ, 2009; Sartika, 2011; Scholz et al., 2016; Yamada et al., 2009) with average intakes of nTFA between 0.18 and 1.35 g day^{-1} for Indonesian and French adults, corresponding to 0.09% and 0.56%, respectively, of the total daily energy intake. France, Spain, New Zealand, and Australia showed a higher intake of nTFA than Japan and Indonesia, with more than half of the nTFA consumed of dairy origin (milk, yogurt, cheese, and butter) and 10–25% of meat origin. Very few countries have data on TFA consumption in different populations (children, adults). French data found that adults and children aged 3 to 17 years have the same energy intake from total TFA but children consume more iTFA than nTFA compared to adults (AFSSA, 2009).

Impact of *trans* Fatty Acids on Health

Due to their three-dimensional structure, TFA easily crystallize at room temperature and behave more like SFA than unsaturated fatty acids. There is a large scientific consensus that consumption of iTFA, principally present in PHO, has detrimental effects both on cardiovascular risk factors

(*i.e.*, blood lipids and lipoproteins, inflammatory markers) but also is associated with risk of CVD (increase of CVD events and mortality) (Mozaffarian et al., 2009; Willett et al., 1993). In addition, it has been demonstrated that replacing TFA with any kind of fatty acids, even SFA, decreases risk of CVD (Mozaffarian et al., 2009). The effect of dietary nTFA on CVD risk marker appears to be very close to that of iTFA (Brouwer, 2016), while their effect on CVD is less known due to the limited number of studies. The impact of dietary nTFA on public health is still a matter of debate, mainly because it is difficult to consume very high levels of nTFA in a typical diet (Mozaffarian et al., 2009). This situation is complicated by the difficulty in reduction of nTFA intake, principally coming from milk and meat. In fact, it is challenging to drastically reduce nTFA content in milk fat (the reduction is accompanied by an increase of SFA, also having a negative health impact) (Kliem and Shingfield, 2016). The alternative could be partial or total removal of dairy fat (*e.g.*, favor the consumption of partially or skimmed milk). The overall health impact of dairy fat is highly debated and, due to the absence of systematic studies about its health impact, no clear recommendations could be drawn to limit its content in foods and diets.

Regulatory Situation

Due to their impact on health, many countries have implemented regulations to limit the consumption of TFA. The FAO/WHO recommends a maximum intake of 1% energy of the daily diet (FAO/ WHO, 2010). In the Global Action Plan for the Prevention and Control of Non-Communicable Diseases for 2013–2020, WHO recommends replacing TFA with unsaturated fat (WHO, 2013). The FAO/ WHO is currently working on updating its 2010 recommendation and opened to public consultation in May 2018 its Draft Guidelines on SFA and TFA intake for adults and children (WHO, 2018). The proposed recommendations for trans fat were overall the same as previously, and it is foreseen that the official Guidelines will be released in 2019 or 2020.

The worldwide regulatory situation on TFA is quite complex because the definition of TFA is not the same in all countries, the labeling requirements are also not the same worldwide and some countries have included or are considering to include limits of TFA in products or banning of PHO (directly or indirectly). The Codex definition of TFA is the most widely accepted worldwide and defines TFA as the geometrical isomers of mono-unsaturated and poly-unsaturated fatty acids having nonconjugated, interrupted by at least one methylene group, carbon–carbon double bonds in the *trans* configuration. This definition includes nTFA and excludes conjugated linoleic acids (CLA).

In 2015, the US FDA announced the decision to withdraw the GRAS status for PHO for any use in human food and has set the deadline of June 2018 for manufacturer compliance. This decision risks to have a large influence all over the world (US FDA, 2015).

In 2010, the European Food Safety Authority (EFSA) has recommended that TFA intake should be as low as possible in the context of a nutritionally adequate diet (EFSA, 2010). There is currently no mandatory labeling nor harmonized legislation on TFA in Europe, but as part of *Regulation (EC) No 1169 / 11* on the provision of food information to consumers, the European Parliament and the Council requested that the European Commission (EC) reports on 'the presence of trans fats in foods and in the overall diet of the Union population. On October 2015 in an open letter to the European Commission, a group of four non-government organizations (NGO) and four major food companies requested the implementation of TFA limits in foods within the European Union (the proposal was to have less than 2 g TFA per 100 g of fat). On December 2015, the European Commission published a report suggesting the introduction of TFA limits in food products and mandatory TFA labeling. Four scenarios have been proposed: (1) No EU policy change; (2) Set TFA limits for iTFA in foods (proposed at 2 g per 100 g product); (3) have mandatory labeling of TFA or (4) ban of PHO in foods. In order to take an informed decision, an impact assessment of these measures has been carried out considering: (1) the economical impact (operational costs, reformulation costs, labeling costs, internal and international competitiveness), (2) the impact on consumer (product offer, health impact, cost impact), (3) the replacement issue (use of palm fat, use of SFA), (4) the administrative burden, and (5) the impact on small companies. On October 2016, the resolution to limit industrial TFA was adopted by European Parliament and on October 2018 the draft EU regulation on iTFA has been published. This regulation foresees the enforcement of a limit of iTFA of 2 g per 100 g of fat. The transition period will be until April 1, 2021.

Countries having set regulatory limits for TFA in food products include Austria, Hungary, Denmark, Lithuania, Norway, Iceland, Latvia, South Africa, Switzerland, Georgia, Peru, Jordan, Romania, UAE, Saudi Arabia, Bahrain, Qatar, Oman, Kuwait, and Yemen. In 10 of these 20 countries, namely Austria, Hungary, Denmark, Lithuania, Latvia, South Africa, Switzerland, Peru, Jordan, and Romania the nTFA are excluded and only iTFA are considered. This list may not be exhaustive, since the regulatory context is rapidly evolving. Canada is discussing the banning of PHO.

Impact of iTFA Removal on Products and Consumers

TFA influence many aspects of food functionalities and their replacement has large impact on taste, texture, oxidative stability, supply chain, cost, handling in factory,

processability, consumer acceptance, nutritional value, and health effects. The alternative solutions to replace TFA should be also considered from a clean label and sustainability perspective.

Based on existing literature and WHO recommendations (see above), we have tried to propose Guiding Principles when products are (re)formulated with the purpose to eliminate iTFA (PHO):

- Whenever possible replace iTFA with MUFA and PUFA.
- Do not replace iTFA with simple sugars.
- The renovated product should not contain more of the "atherogenic" fatty acids per total product weight, i.e., lauric (12:0) + myristic (14:0) + palmitic (16:0) acids, than the original product, if possible less.
- When removing PHO, SFA should not increase, and whenever possible SFA should go down
- Linolenic acid (18:3) should be favored over linoleic acid (18:2), if possible.

The reformulation efforts require a multi-stakeholder approach and transparency all along the value chain. In particular, the following aspects are important success factors:

- Shared and harmonized analytical methodology to guarantee comparable data between suppliers, food companies, and governments.
- Research efforts to provide possible alternatives, both at fat and oil supplier and food industry level.
- Technical understanding of possible solutions and their limitation.
- Investments in manufacturing changes and transport costs.
- Update of raw material specifications.
- Regular compliance testing after re-formulation.
- Large clinical trials organized by academia, government, and/or industry to investigate the health impact of possible alternatives.
- Evolution of the regulatory framework.

Lessons Learned and Way Forward

The story of TFA offers many learning points. It started at the beginning of the 20th Century with the development and implementation of the hydrogenation technology to produce solid multifunctional fats. During the years, the negative impact of the byproducts of hydrogenation, iTFA, became clear and has led to the recommendation to reduce or eliminate this technology, after almost 100 years of usage. Those events have had two important consequences: (1) negative public health impact and consequently financial impact for health care costs due to the extensive use of PHO and (2) financial costs for the elimination of PHO, both sustained by Governments (*e.g.*, regulatory costs) and by private industries (costs of reformulations). In addition, it has had an impact on consumer trust and clarity about nutritional recommendations. A post-mortem analysis could avoid repeating the same experience with other raw materials. For instance, we could draw the following principles and recommendations:

- The scientific community should carefully scrutinize embracement of new technologies and clinical results of studies related to these new technologies in order to avoid choices, which might have negative impact on population health and high financial cost for correction/reformulation.
- An appropriate regulatory framework is needed to create a level-playing field and trigger innovation.
- *Nutrition by Design* for new ingredients & new products is necessary. When considering a (re)formulation, the impact of all the alternatives and the replacement ingredients should be carefully considered in order to prevent unexpected future negative health impact.
- Finally, *Sustainability by Design* is a key element to consider during product development. We need to hit the sweet spot between nutrition, sustainability (good for the planet), and technological characteristics of lipids.

Looking forward, the fats and oil industry and food manufacturers are facing important problems that need a multi-stake-holder approach:

- Mitigation of bound 3-monochloropropane-1,2-diol or 3-chloropropane-1,2-diol; 2-monochloropropane diol (MCPD)/glycidol;
- Understanding and improvement of the sustainability of most used crops, including soya, palm, rapeseed, and cotton;
- Understanding not only the health effect of single fatty acids (oleic, stearic, linoleic, EPA and DHA acids) but also that of oils and fats and the role they play in "Healthy Food Patterns" (as suggested in the latest Dietary Guidelines for Americans (Dietary Guidelines Advisory Committee, 2015).
- Finally, several surveys have highlighted that consumers are highly confused about fats and oils: they do not understand the differences between health effects of different types of fat nor do they know the sources of different types of fats (IFIC, 2012). More consumer education is needed to avoid confusion and promote healthy eating.

How Industry Is Adjusting with Recent Changes in the Regulations Related to Lipids and Fat

Diliara Iassonova

History

In the past 30 years, food industry experienced two major shifts and reformulations of fats and oils as a result of government agencies recommendations and regulatory requirements. Highly saturated fats such as animal fats (lard and tallow) and palm oil dominated in food applications globally until early 1990s when several scientific reports linked SFA consumption to cardiovascular disease and resulted in regulatory requirements for labeling saturated fat and cholesterol. Industry migrated out of highly saturated fats to PHO. Partially hydrogenated oil production was a mature and relatively simple technology that allowed the production of custom-made fats for target applications. In fact, first reformulation from highly saturated fats to PHO went relatively fast and easy because PHO delivered over 50% SFA reduction, was widely available, economical, and had additional benefits such as functional performance, versatility, and oxidative stability. However, shortly after it was discovered that TFA from PHO had worse impact on human health than SFA did (Judd et al., 1994; Mozaffarian et al., 2009). New requirements of zero trans-fat per serving resulted in second reformulation from PHO to "zero trans-fat" solutions that started in early 2000s.

Product-Specific Applications

Snack industry led the change by replacing PHO with liquid oils with natural and synthetic antioxidants (Van Camp et al., 2012). Vegetable oils with synthetic antioxidants such as tertiary butylhydroxyquinone (TBHQ), butylated hydroxytoluene (BHT), and butylated hydroxyanisole (BHA) were relatively economical PHO replacement solutions that delivered shelf life expectations in snack applications. Unfortunately, TBHQ, BHT, and BHA are regulated additives and linked to the cancer risk at levels >200 ppm (Shahidi and Zhong, 2005). Oil blends with tocopherols and rosemary extracts were also commonly used as "clean" label "zero trans-fat" solutions in snack applications.

The most challenging PHO reformulation was in bakery application because PHO provided an economical, oxidatively stable source of "beta-prime" shortenings with structure and functionality that are essential for performance in bakery products.

Many bakery manufactures switched back to palm-based shortenings; however, nutritional concerns for replacing trans-fat with SFA and higher functionality expectations that versatile PHO products set forced industry to search for more sophisticated "zero trans-fat" solutions. After over decade of development, fats and oils suppliers drastically expanded portfolio of structured "zero trans-fat" shortenings to meet bakers' need in functional, economical, sustainable, oxidatively stable, and label-friendly fats.

Commercially successful PHO reformulation solutions for bakery fats can be divided into three major groups based on technologies used to replace trans-fat:

- Shortenings made with palm oil and its fractions are dominant on the market. Palm oil is the most widely available and economical structured fat and the development of fractionation technology expanded opportunities for formulators even further. A wide range of palm-based products are available on market, as well as variety of palm-based products formulated with liquid oils and structuring agents to improve palm oil consistency, shelf stability, functionality, and decrease saturated fat content per serving.
- Shortenings made via physical blending with fully hydrogenated fat. Majority of low-saturated offerings on the market are represented by shortenings made from liquid commodity or high stability vegetable oils blended with fully hydrogenated oils. These are then manufactured using votation or scraped surface heat exchangers to ensure shortening structure and solid fat content for performance as bakery fats. These solutions are typically less than 35% saturated fat and do not contain palm oil, but often have limiting factors such as product consistency, lower oxidative stability if formulated with commodity oils, and the hydrogenated fat ingredient should be reported on the label.
- Interesterified shortenings are made via rearranging fatty acids within triacyclglycerols of oil blend containing liquid oil and "hard stock" using base catalyst (chemical interesterification) or enzymes (enzymatic interesterification). Fully hydrogenated fats (soybean or cottonseed) as well as palm stearin are typically used as "hard stock". Interesterified solutions still have relatively limited but growing market share, offering bakers consistent functionality and oxidative stability.

Partially hydrogenated oil replacement in frying applications (industrial and restaurant) was less challenging than in bakery applications because the majority of fats and oils can be used as frying oil. However, PHO replacements had set expectations for oxidative stability, cost, and shelf life along with "0 grams trans-fat per serving.". Commodity oils like soybean and canola were a relatively economical PHO replacement for frying but less stable and had limited frying performance compared to PHO. Restaurant operators faced multiple problems when switching to less stable oils with high percent of polyunsaturated fatty acids (PUFA), including inconsistency in fried product flavor and texture, increase in polymer formation that deposited on equipment and was hard to clean, faster oil smoking, and darkening as a result of fast oil degradation. As an alternative, variety of

votated blends of liquid oils with fully hydrogenated oils, named "creamy" after its appearance, were developed as a PHO replacement for frying applications, and performed better than commodity oils. Creamy solutions delivered "0 g trans-fat per serving" claim and had a slightly higher SAFA content than base oil, typically less than 5% fully hydrogenated fat added in creamy solution. As opposed to partially hydrogenated fat, fully hydrogenated fat does not contain significant amounts of TFA; however, consumers do not differentiate "partial hydrogenated" from "fully hydrogenated"; in fact, majority follows the logic if "partial" is bad then "fully" even worst. Products with fully hydrogenated oils in the ingredient list are expected to receive more consumer pressure and will be formulated out after 2018, when PHO is no longer GRAS (US FDA, 2015).

Unlike bakery applications, palm oil and palm oil fractions did not receive wide use in frying applications in North America and Europe as a PHO replacement. Palm oil is a high-performance frying oil, but saturated fat content, sustainability and recently 3-MCPD and GE contaminants concerns were its limiting factors.

Despite unique frying flavor and frying performance comparable to PHO, animal fats had limited market share as a PHO replacement due to high saturated fat content.

Development of Alternative Oils and Fats for Replacing PHO

Partially hydrogenated oil reformulation identified the need for high stability, high performance, healthy oils, and stimulated specialty oils development programs. These market forward innovations were focused on nutrition and functional performance of the novel oils. After decades of development via conventional breeding and/or transgenic technology, several specialty oils were commercialized including high and mid-oleic sunflower, high oleic safflower, low linolenic, and high oleic soybean and high oleic canola oils.

In North America, high oleic canola oils (Clear Valley and Natreon) are by far the most commercially successful "0 grams trans-fat per serving" PHO replacement solutions among all specialty oils especially in frying and snack applications (DeBonte et al., 2012). High oleic canola (HOCAN) oils are high oxidative stability oils with clean, slight nutty flavor, and low saturated fat content (Table 1). HOCAN oils made from non-GMO or GMO seeds are available globally. In frying applications, HOCAN are distinguished by their long frying life and sensory performance of fried products (Liu, 2014). The new member of the HOCAN family is Clear Valley Low Saturated High Oleic Canola Oil, which has the lowest (less than 4.5%) saturated fat content among all commercially available oils, a high oxidative stability and clean flavor.

Mid-oleic (NuSun) and high oleic sunflower (HOSUN) oils are another example of PHO replacement solutions that are mainly used in snack applications with Non-GMO claims in North America. Specialty sunflower oils have a smaller but growing market share in North America, but HOSUN is commonly used as single oil or in blends for frying and snack applications with a long shelf life in Europe.

Two novel high oleic soybean (HOSOY) oils, Vistive and Plenish, were developed via transgenic technology. Both oils are high stability oils, especially Plenish with an oxidative stability over 26 hours at 110 °C and have a potential for frying and long shelf life applications.

Nowadays, PHO solutions are developed for all major applications including bakery, snacks and frying. Food industry response to the regulatory requirements, trends, and consumer awareness resulted in the following:

1. Diversification of fats and oils solutions including blends, modified fats, and complex fat systems;
2. Development of new specialty oils;
3. Development of new solutions with fully hydrogenated vegetable oils.

Palm and palm fractions are the major replacement of PHO in bakery applications, whereas HOCAN oils are the most successful PHO replacement in frying applications. Today fats and oil suppliers offer wide range of PHO replacement solutions that deliver target functional performance, shelf life, cost, ingredient, and labeling expectations and were accepted by processed food industry. Partially hydrogenated oil reformulation can be considered completed (Downs et al., 2017). The next targets for developers have been identified by consumer trends such as clean label and processing solutions.

The New Toxic Substances Control Act in the US: Impact on Lipids

Lynn L. Bergeson

The Toxic Substances Control Act (TSCA) is the federal law that regulates industrial chemical substances used in applications *other* than food, drugs, cosmetics, and pesticides, or other uses that are regulated by other federal authorities.[1] TSCA was significantly amended in 2016, and

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Table 1 Specialty vegetable oils composition (major fatty acids %) and oxidative stability (OSI hr. at 110 °C)

	OSI at 110 °C	Saturated (%)	Oleic 18:1 (%)	Linoleic 18:2 (%)	Linolenic 18:3 (%)
Clear Valley 65	15	7	66	22	<3
Natreon	17	7	73	15	<3
Clear Valley 75	>17	7	75	14	<3
Clear Valley 80	>20	7	80	8	<2.5
Clear Valley Low Saturate	>17	<4.5	71	21	<2.5
Mid Oleic Sunflower NuSun	>9	10	>60	26	0.5
High Oleic Sunflower	>17	8	>80	<8	<0.5
High Oleic Soybean Oil Vistive	>17	6	71	19	<3.0
High Oleic Soybean Oil Plenish	>26	11	78	7	2

American Oil Chemists' Society (AOCS) members need to understand how TSCA applies to fats and oils that have commercial application as fuels, industrial intermediates, and/or applications, and generally appreciate the implications of new TSCA on their commercial operations. Doing so will better assure uninterrupted business operations and consistent TSCA compliance.

TSCA Basics

TSCA authorizes the U.S. Environmental Protection Agency (EPA) to regulate "chemical substances" (US EPA, 1976a), defined broadly to include "any organic or inorganic substance of a particular molecular identity" (US EPA, 1976b; US Office of the Federal Register, 2018a, 2018b). The term "chemical substance" as defined does not include pesticides, drugs, and food, which are regulated under other federal laws (US EPA, 1976c). A chemical substance for TSCA purposes includes plant or animal-derived substances and microbes used for TSCA purposes. TSCA is a complicated law with many interesting provisions and fascinating policy implications. The focus here on aspects of two TSCA sections, Section 8(b)(1) and Section 5, as an understanding of these provisions is critical to understanding how TSCA applies to fats and oils that are substances of biological or microbial origin.

TSCA Section 8(b)(1): The Chemical Inventory

TSCA Section 8(b)(1) directs EPA to compile and keep current a list, commonly referred to as the TSCA Chemical Substance Inventory, of each chemical substance that is domestically manufactured or imported into the U.S. (US EPA, 1976d). The initial Inventory was developed from 1978 to 1979 using input from the chemical industry that allowed "existing" chemical substances already in commerce to be "grandfathered" into the Inventory. These chemicals were included on the TSCA Inventory automatically, side-stepping any EPA review of them at the time of the listing. The Inventory is significant because if a chemical is not included on the Inventory, and is not otherwise exempt, the commercial production, distribution, and use of the substance are impermissible.

The TSCA Inventory is divided into two parts: the publicly accessible nonconfidential Inventory that is readily accessed using the Chemical Abstracts Service (CAS) Registry Numbers (CASRN) for chemical substances; and a confidential Inventory accessible only by EPA through its TSCA Inventory Master File. In the case of substances listed on the confidential portion of the Inventory, a generic name that masks the specific chemical identity of the substance and an accession number are placed on the nonconfidential portion of the Inventory, and the specific chemical name is placed only on the confidential portion of the Inventory.[2]

New chemical substances (any substance not listed on the TSCA Inventory or otherwise exempt from listing) may be added to the TSCA Inventory via a process that involves submission of a Premanufacture Notification (PMN) or a Microbial Commercial Activity Notice (MCAN) for microbes, as described below. EPA typically reviews approximately 1000 or so new chemical substances each year.[3] Once EPA completes review of the new chemical and imposes any needed regulatory requirements, the notifier is permitted to commence import or manufacture; the

[2] The confidential portion of the Inventory can only be accessed in two ways. First, one could submit a PMN for the substance in question, because upon receipt of the PMN the first action by EPA will be to search the existing public and confidential inventories to determine whether a PMN is needed for the substance. Second, a confidential listing may be found by submitting a bona fide request to EPA, requesting whether the substance in question is present on the confidential Inventory (US EPA, 1976e).

[3] Section 5 of TSCA prohibits the manufacture or import of a new chemical substance for a nonexempt commercial purpose unless the substance has been the subject of a PMN submitted at least 90 days before commercial manufacture or import commences (the notification period may be extended to 180 days by EPA under certain circumstances).

notifier must then submit a Notice of Commencement (NOC), receipt of which triggers EPA to add the chemical substance to the Inventory, transforming it into an existing chemical substance. Adding chemicals to the Inventory has always been challenging, but it is more so today as a consequence of the 2016 TSCA amendments. These challenges are especially daunting to entities wishing to use an expanded array of fats and oils derived from sources not specifically listed in the TSCA Inventory, as discussed below.

TSCA Section 5: Chemical Notification

TSCA Section 5 governs the manufacture in and import into the U.S. of chemical substances considered "new." As noted, manufacturers (a term that includes importers) of chemical substances considered new must notify EPA of the new chemical substance through the submission of a PMN or MCAN (US EPA, 1976f).[4] Unless a PMN exemption applies,[5] a company must submit a completed PMN form to EPA at least 90 days before commencing the manufacture or import of a new chemical substance. Although the statutory minimum is 90 days, in practice a company should allow more time for PMN or MCAN review.

Amended TSCA retains much of old TSCA Section 5 but makes significant changes that are proving challenging where notifications have not been prepared strategically, thoughtfully, and comprehensively. Under revised Section 5(a)(3), EPA is required to review all new chemical notifications (both PMN for conventional chemicals and MCAN for microorganisms) and Significant New Use (SNU) notifications, and make one of three determinations and take required actions, as outlined below, depending upon the determination. In evaluating whether an "unreasonable risk" is presented by such cases, EPA is required to consider potentially exposed or susceptible populations identified as relevant and, in some cases, this includes the concept of "under the conditions of use." EPA is also required to undertake a staged review focusing initially on the determination and then on the action required given the determination made. As is true generally under new TSCA, as part of this staged process, EPA is disallowed from considering cost or other non-risk factors in determining whether a chemical presents an unreasonable risk.

This approach to new chemical review represents a fundamental departure from old TSCA. Previously, new chemical innovators submitted a notice under TSCA Section 5 and if 90 days passed without EPA action, the submitter could commence chemical production or import followed by the submission of an NOC. Under new TSCA, this passive approach has been replaced by an active one and an EPA determination is required along with any needed regulatory actions as a predicate to commercial production.

In satisfying the requirement that EPA make a determination and take required actions on all new chemicals and SNU, there are three alternative determinations available to EPA under new TSCA. First, EPA can determine that the new chemical or SNU presents an unreasonable risk of injury to health or the environment, in which case, EPA is required to regulate under Section 5(f) and must then also promulgate a Significant New Use Rule (SNUR) or explain why not.

The second alternative consists of a series of "or" statements. EPA can determine the information available on the chemical is insufficient to permit a reasoned evaluation of the health or environmental effects of the chemical, **or**, in the absence of sufficient information, the substance may present an unreasonable risk, **or** that the substance will be produced in substantial quantities and it either enters or may be anticipated to enter the environment in substantial quantities, or that there is or may be significant or substantial human exposure. If any of these determinations is satisfied, EPA is required to issue an order under Section 5 (e) and either to implement a SNUR or explain why it is not taking this step.

The third determination EPA can make is that the new chemical or SNU is not likely to present an unreasonable risk, in which case, the notice submitter can commence manufacture/processing forthwith once the determination

[4] EPA's PMN regulations appear at 40 C.F.R. Part 720 (US Office of the Federal Register, 2018c), and several PMN exemptions are contained in 40 C.F.R. Part 723 (US Office of the Federal Register, 2018d).

[5] There are exemptions from the requirement to submit a PMN. Exemptions are either "self-executing" or require prior EPA approval. Self-executing exemptions are those that take effect once an entity determines that the exemption applies, and the new chemical substance can be manufactured in the U.S. without the need for a PMN, provided the company complies with any recordkeeping or other applicable requirements for the particular exemption. Self-executing PMN exemptions include the exemption for chemical substances having no separate commercial purpose, the polymer exemption, and the research and development (R&D) exemption. Other exemptions from the PMN requirement require prior EPA approval. Entities must submit, and EPA must approve, an exemption application before the entity can commence manufacture of the new chemical, subject to compliance with any recordkeeping or other applicable requirements. PMN exemptions that require prior EPA approval include the low volume exemption (LVE), the low release and low exposure exemption (LoREX), and the test marketing exemption (TME). Eligibility for an LVE is based on the manufacture of a new chemical in quantities of 10,000 kg or less per year, while eligibility for a LoREX is based on meeting several regulatory criteria for "low" release and exposure throughout the manufacture, processing, distribution, use, and disposal of the chemical (US Office of the Federal Register, 2018e, 2018f). One kilogram is equivalent to 2.2 pounds. Once EPA notifies an applicant that its LVE or LoREX application has been granted, or if the 30-day review period expires without notice from EPA, manufacture or import of the chemical substance may commence, consistent with the terms of the exemption. *Id*. § 723.50(g)(2). US Office of the Federal Register, 2018g).

has been made, notwithstanding any remaining portion of the applicable review period. EPA is also required to publish a statement of its finding. This determination and its statement are not legally reviewable.

Chemical Identity Issues Specific to Lipids

When preparing a PMN or MCAN submission, it is critical that attention be paid to the substance identity, as it can affect the TSCA regulatory status of the substance and its downstream products as new or existing substances. For substances with a single, well-defined chemical structure, such as ethanol and acetic acid, the naming conventions and TSCA Inventory search are relatively straightforward. The precise determination of the chemical identity and TSCA Inventory status of a substance lacking a definitive molecular formula or structural diagram can be more complicated. These less-defined substances, referred to as Class II chemicals, include "unknown or variable composition, complex reaction products, or biological materials" (UVCB). UVCB substances are often identified by the "source" and chemical processes used during manufacturing. The source-based nomenclature system results in multiple nomenclature listings for nearly equivalent chemical substances that are derived from different sources.

For example, soybean, canola, and sunflower oil are each listed separately on the TSCA Inventory and a company cannot rely on any of these listings to manufacture or import an oil from another source. Companies should also be aware that the Class II nomenclature system propagates through the supply chain, for example, if each of the soybean, canola, and sunflower oils are converted to fatty acid methyl esters (FAME), the individual FAME are listed separately (*e.g.*, fatty acid, sunflower, Me ester). This so-called "source-based" system has significant business implications for AOCS members and other stakeholders. Source-based identities include: soybean oil; fatty acids, soya; fatty acids, soy, ethoxylated; corn oil; fatty acids, corn-oil; and fatty acids, corn-oil, ethoxylated.

In 1979, EPA attempted to streamline the Class II nomenclature system by developing a source-agnostic system with the help of the Soap and Detergent Association (SDA) (now the American Cleaning Institute). The SDA nomenclature system, which is based on substance type and alkyl range rather than source and processing, allows for significantly expanded feedstock and operational flexibility by drawing equivalence between chemical substances produced from 35 natural sources of fats and oils and their petroleum-based counterparts, but limits eligibility to these sources (US EPA, 1979). Note that the SDA policy states "Alkyl groups derived from other natural sources are not covered by this system." EPA interprets this statement to mean that sources that are not listed are not eligible to use the SDA nomenclature.

Sources not eligible for SDA nomenclature include tall oil, jatropha oil, camelina oil, waste oils and grease, algal oils, and oils produced by Genetically Modified Organisms (GMO). It means that the manufacturer of a novel source chemical substance (*e.g.*, algal oil) is required under TSCA to submit to EPA a chemical notification under TSCA Section 5 to add the substance to the TSCA Inventory before commercializing the material. Even more consequential is the fact that the manufacturer's customers may also be required to submit a PMN for downstream UVCB substances that are produced from it, such as free fatty acids and biodiesel. The time and business planning that it takes to accomplish these inconvenient realities cannot be over-emphasized, especially now that new TSCA requires a more disciplined and time-consuming review of new chemical notifications.

SDA Nomenclature Source

Table 2 lists the 35 natural sources of fats and oils identified in 1979 by EPA, with SDA's assistance. Chemical substances derived from these sources and their petroleum-based counterparts are eligible for equivalence between chemical substances. As noted, even though two oils may be used interchangeably because they have similar fatty acid profiles, the different sources mean they have different chemical identities for TSCA purposes. Thus, if they are not listed in Table 2, feedstock flexibility among natural fats and oils and their petroleum-synthetic equivalents is greatly diminished.

New TSCA provides EPA with authority to recognize multiple listings of a substance listed on the Inventory as a single substance. EPA is not mandated to exercise this authority, but discussions between industry and EPA are underway to achieve this goal. To support the efficient commercialization of bio-based products, the microbial chemical industry would be wise to engage with EPA to ensure that consideration is given to a wider range of sources, not just the ones that were available in 1979. Expansion along these lines would facilitate operational flexibility and level the playing field for new product entrants that are based on sources that fall outside the listed 35 natural sources, but have compositions that are largely, if not entirely, the same as those existing natural sources.

Reporting Exemptions

Naturally occurring substances are exempt from Section 5 reporting since EPA considers such substances to be automatically listed on the TSCA Inventory (US Office of the Federal Register, 2018h). This category of substances is

Table 2 Source: EPA, Toxic Substances Control Act (TSCA) PL 94-469, Candidate List of Chemical Substances, Addendum III: Chemical Substances of Unknown or Variable Composition, Complex Reaction Products and Biological (US EPA, 1978)

	Vegetable	Animal	Marine
Avocado	Peanut	Grease	Herring
Babassu	Rapeseed	Lard	Menhaden
Castor	Rice Bran	Neatsfoot	Salmon
Coconut	Safflower	Poultry	Sardine
Corn	Safflower (high oleic)	Tallow	Sperm body (whale)
Cottonseed	Sesame		Sperm head (whale)
Crambe	Sorghum		Whale
Linseed	Soybean		
Olive	Sunflower		
Oiticica	Tung		
Palm	Wheat Germ		
Palm-kernel			

These sources provide both saturated and unsaturated alkyl groups; castor oil provides a C18 hydroxy substituted group. Alkyl groups derived from other natural sources are not covered by this procedure.

important to stakeholders for reasons that need no explanation. EPA has defined "naturally occurring" substances quite narrowly, however, and care should be taken to understand its scope for TSCA purposes. Microorganisms that do not contain genetic material from organisms of a different taxonomic genus may be considered naturally occurring, whereas intergeneric microorganisms are not naturally occurring. Importantly also, the processing of a microbe or other bio-based substance beyond the discrete methods described in the definition of naturally occurring substances (*e.g.*, manual or mechanical processing) likely results in a substance that EPA would not consider naturally occurring and thus exempt.

Depending on their end use, intergeneric microorganisms, feedstocks, intermediates, byproducts, enzymes, and other catalysts may all be reportable under TSCA. Furthermore, companies that rely on byproducts or waste as a feedstock should engage with their supplier regarding the TSCA status of the feedstock to avoid undue supply delays. For example, yellow grease (waste glycerides from kitchen uses) is listed on the TSCA Inventory, so it may be used as a feedstock for growing microbes for a non-exempt TSCA purpose. Brown grease (waste glycerides from sewage treatment), however, is not listed on the Inventory, so EPA likely would be of the view that a bioeconomy company could not use brown grease as a feedstock for a commercial purpose regulated under TSCA without additional regulatory action.

Additional TSCA Provisions

The fats and oils chemical industry may also be interested in some of the more general provisions that were introduced as part of new TSCA. For instance, Section 14 now requires that companies substantiate many confidential business information (CBI) claims at the time the confidential information is submitted to EPA (US EPA, 1976g). The substantiation process takes time; careful consideration and a rigorous process must be part of the business process to ensure that confidential information is protected.

New TSCA also modified Section 14 to make it explicit that some information is not protected from disclosure, including mixed confidential and non-confidential information, general descriptions of the manufacturing, and/or processing and aggregated production volumes (US EPA, 1976h). Companies should also be aware that health and safety studies cannot be protected as CBI (although the identity of the test substances may be confidential, if justified). Additionally, new TSCA requires EPA to consult with the Small Business Administration (SBA) to review the adequacy of the current standards for small manufacturers and determine whether a revision of the definition of a "small" business is warranted, which EPA has done (US EPA, 1976i).

Tips to Consider

The full implications of new TSCA will become clearer as EPA fully implements its new authorities and EPA's deployments of these authorities are judicially refined. It is crucial that AOCS members and other stakeholders are familiar with TSCA's statutory provisions and EPA's implementation of them, and engage meaningfully and robustly in implementation activities that impact the development, regulation, and commercialization of chemical products. A thorough understanding of EPA's approach to chemical regulation is key to avoiding commercial

disruptions and operation delays, competitive imbalances, and potential assertions of noncompliance.

Companies are also encouraged to develop a strong compliance program, to consider the regulatory timeline when formulating business plans, and to seek assistance from experts in the regulatory and legal fields regarding the preparation and review of EPA submissions. Innovators are encouraged also to develop strong relationships with regulators based on trust and clear and open communication. Regulators are a critically important component of the stakeholder community and are often under-appreciated as one of a business' strongest supporters. While EPA may recognize and be receptive to the benefits of animal and plant-based products, it is still required to regulate such chemical substance if it determines that the substance may present unreasonable risk during the review process. Engaging with EPA early in the process to understand any potential concerns, how those concerns can be addressed, and how a product's pollution prevention attributes provide essential value to the economy may help companies avoid significant regulatory issues and potentially costly business delays down the road. Below are a few tips to help ensure consistent compliance and predictable business operation:

Ensure TSCA Compliance Is a Core Element of the Business Plan

The first piece of advice we offer is to know the TSCA requirements, understand the regulatory responsibilities, and be prepared to meet both the requirements and the responsibilities as a part of a business development plan. TSCA provisions should not be collateral to the business plan; they must be a core element embedded in the planning process. A good command of TSCA will decrease the likelihood of a major, unanticipated disruption to the commercialization timeline due, for example, to late recognition of the need for a PMN, MCAN, or other significant premarket issue.

Understand the Relevance of Chemical Naming

It is critically important to recognize and understand the importance of how a chemical substance is named and identified for TSCA purposes, and how that identity is determinative to a manufacturer's responsibilities. As discussed above, there is both art and science involved in naming a TSCA chemical. It is important to understand the relevance of naming conventions to the manufacturing process. If this core competency does not exist within the company's staff, find competent professionals who can guide this important process. As arcane as this point may seem, it could make a critical difference in the timing of the commercialization process.

Know the Fundamentals of the TSCA Review Process

A basic understanding of EPA's review process and regulatory approach is essential. While EPA works off of the information included in the PMN/MCAN, it also considers information on other "related" cases, applies quantitative structure–activity relationships ([Q]SAR) analysis when hazard test data are not available, and, inter alia, will use assumptions about potential exposures and releases if information is not provided in the notification. EPA also has a number of policy drivers that can affect new chemicals, including its use of "categories" of PMN, the persistent, bioaccumulative, and toxic (PBT) policy, and the exposure-based policy for new chemicals.[6] It is useful to understand and be able to anticipate (and where possible, avoid) the potential effect of these policy drivers.[7]

Consider Testing in Advance of PMN/MCAN Notification

If EPA is likely to impose testing requirements on a bio-based new chemical, consider the benefits of either doing the testing in advance of the notification (and thus avoiding that issue), or, if future commercialization plans involve additional structurally similar new chemicals, whether it might make sense to develop a testing strategy that would attempt to encompass and account for the range of new chemicals likely to be introduced. While such a strategy could be implemented by a single company, if other firms are known to be active in this area of new chemical development, there might be significant cost saving and advocacy opportunities for organizing consortia to share the costs and responsibility of testing. EPA is also more likely to be receptive to a consortium's regulatory advocacy, as opposed to a single company's efforts to influence new

[6] A thorough review of these policies is beyond the scope of this paper. It is important to recognize, however, that EPA's chemical management program and TSCA review process is premised upon a number of important policies. For example, in 1999, EPA issued its final policy statement on a category of PBT chemicals. (US Office of the Federal Register, 2018i). The policy statement reflects EPA's policy regarding PBT chemicals, and advises industry about EPA's regulatory approach for chemicals meeting the criteria of a PBT chemical. Another important policy is EPA's approach to chemical categories. EPA groups a chemical with shared a chemical and toxicological properties into categories. According to EPA, this enables PMN submitters and EPA reviewers to benefit from collected data and "past decisional precedents" in the PMN review process. What this means in practice is that if PMN submitters are unaware of the chemical categories approach, essential elements of EPA's approach to the review of a particular PMN submission may be overlooked in the preparation of the PMN and critical missteps could compromise the success of the PMN, resulting in lengthy delays or fatal mistakes. For information on EPA's New Chemicals Programs, see US EPA 2018a?

[7] For an overview of the PMN process, *see* EPA, Filing a Pre-manufacture Notice with EPA (US EPA, 2018b).

chemicals policy. Any testing strategy should include consideration of future market opportunities (*e.g.*, the European Union), so that registration requirements imposed by other countries can be addressed or satisfied with the testing performed to support a TSCA notification.

Work with EPA

Regardless of the approach taken, it is always wise to consult with EPA before embarking on chemical-specific testing or developing and implementing a testing strategy. This will ensure an understanding of EPA's views on and obtain its receptivity to the approach proposed.

Acknowledgments Fabiola Dionisi and Mathilde Fleith acknowledge S. Barlatey, M.-F. Pagerey and B. Vandewaetere.

Conflict of Interest The authors declare that they have no conflict of interest.

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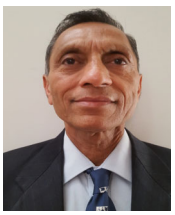

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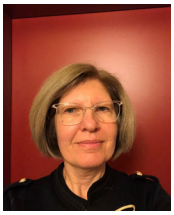

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