

COMMENTS
OF THE
STYRENE INFORMATION RESEARCH CENTER, INC.,
GROCERY MANUFACTURERS ASSOCIATION,
INTERNATIONAL FOOD ADDITIVES COUNCIL, AND
THE SOCIETY OF PLASTICS INDUSTRY, INC.

FOR

DOCKET NO. FDA-2015-F-4317

81 Fed. Reg. 42 (Jan. 4, 2016)

May 3, 2016

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I. Introduction and Summary

A group of non-governmental organizations (NGOs)¹ filed a Food Additive Petition (FAP) with the U.S. Food and Drug Administration (FDA) for which a notice of filing was published in the Federal Register on January 4, 2016. The petition seeks to: (1) remove the existing clearances in 21 C.F.R. § 172.515 for seven different synthetic flavoring additives used in food and (2) establish a zero tolerance for these substances when used as flavoring agents in food. The petition maintains that the review by the National Toxicology Program's (NTP) Report on Carcinogens (RoC) and a Monograph by the International Agency on Cancer (IARC) require FDA to delist the seven substances because the regulation permitting their use is in violation of Section 409(c)(3)(A) of the Federal Food, Drug, and Cosmetic Act (FD&C Act or the Act).

The Styrene Information and Research Center, Inc. (SIRC),² Grocery Manufacturers Association (GMA),³ International Food Additives Council (IFAC),⁴ and the Society of Plastics Industry, Inc. (SPI)⁵ appreciate the opportunity to submit written comments for consideration by the Agency. Although SIRC will provide information to FDA that styrene is not used as a flavorant or

¹ The NGO's include the: Center For Science in the Public Interest, Natural Resources Defense Council, Center for Food Safety, Consumers Union, Improving Kids' Environment, Center for Environmental Health, Environmental Working Group, Environmental Defense Fund, and James Huff.

² SIRC was formed in 1987 as the principal focal point for public information and research on styrene. SIRC is a non-profit organization consisting of voting member companies involved in the manufacturing or processing of styrene, and associate member companies that fabricate styrene-based products. Collectively, SIRC's membership represents approximately 95% of the North American styrene industry. SIRC has gained recognition as a reliable source of information and scientific research on styrene that supports reasoned regulatory decisions. For more information, visit <http://www.styrene.org/>.

³ GMA is the trade organization representing the world's leading food, beverage and consumer products companies and associated partners. The U.S. food, beverage and consumer packaged goods industry has facilities in 30,000 communities, generates \$1 trillion in sales annually, contributes \$415 billion in added value to the economy every year and is the single largest U.S. manufacturing industry with 1.7 million manufacturing workers. Founded in 1908, GMA has a primary focus on product safety, science-based public policies and industry initiatives that seek to empower people with the tools and information they need to make informed choices and lead healthier lives. For more information, visit gmaonline.org The \$2.1 trillion food, beverage and consumer packaged goods industry employs 14 million U.S. workers, and contributes over \$1 trillion in added value to the nation's economy.

⁴ IFAC is a global association representing manufacturers of food ingredients. IFAC strives to promote science-based regulations, standards and specifications for food ingredients worldwide.

⁵ Founded in 1937, SPI: The Plastics Industry Trade Association promotes growth in the \$427 billion U.S. plastics industry. Representing nearly one million American workers in the third largest U.S. manufacturing industry, SPI delivers advocacy, market research, industry promotion, and the fostering of business relationships and zero waste strategies.

adjuvant in food and supports removal of styrene from Section 172.515 based only on abandonment (a petition requesting FDA to remove the listing of styrene based on abandonment was filed on May 3, 2016), SIRC, GMA, IFAC, and SPI oppose FDA delisting any substance based solely on classifications in the NTP RoC or the IARC Monograph. Any decision by FDA that a substance is a carcinogen must be based on a thorough and independent FDA assessment. In addition, FDA should not adopt a zero tolerance policy, particularly for substances such as styrene, which are naturally occurring in food.

In summary, these comments argue that:

- Consistent with its obligation under the Federal Food, Drug, and Cosmetic Act and longstanding Agency practice, FDA should continue to independently evaluate the safety of food additives.
- There are inherent limitations to third party reviews based on: (1) differing objectives and processes for the reviews, (2) the evolution of scientific evaluation criteria and Agency science policy, and (3) the publication of not previously reviewed studies.
- An independent FDA assessment may differ from NTP or IARC's conclusions based on an objective review of the available data.
- A zero tolerance policy is infeasible for a naturally occurring and reasonably ubiquitous substance. Quite understandably, substances that occur naturally in foods contribute to the food's flavor and some substances may be produced as a metabolite in the processes of making some foods, such as cheeses, or as a byproduct of roasting, such as coffee. Collectively, this makes compliance with and enforcement of a zero tolerance policy infeasible.

II. FDA should fulfill its statutory duties and continue its longstanding practice of independently evaluating the carcinogenicity of food additives consistent with the Federal Food, Drug, and Cosmetic Act

The NGOs cite Section 409(c)(3)(A) of the FD&C Act, or 21 U.S.C. § 348(c)(3)(A), as a legal basis for their requests that the seven flavorants be delisted in the FAP. Section 409(c)(3)(A), which is commonly known as the "Delaney Clause", states as follows:

[N]o such regulation [authorizing use of a food additive] shall issue if a fair evaluation of the data before the Secretary . . . fails to establish that the proposed use of the food additive, under the conditions of use specified in the regulation, will be safe: Provided, That no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animal. . . .

Thus, under the Delaney Clause, FDA is prohibited from establishing a regulation for the use of a food additive that has been shown to be carcinogenic in either humans or animals.

The NGOs cite reviews conducted by different scientific bodies as evidence for the proposition that the seven chemicals have been found to induce cancer in humans or animals. In particular, the FAP cites two reviews conducted by the Department of Health and Human Services' (HHS) NTP and IARC for the proposition that the clearances in Section 172.515 violate the Delaney Clause.⁶ For example, with respect to styrene, The NTP⁷ and IARC⁸ reviews categorize styrene as “reasonably anticipated to be a human carcinogen” and as “possibly carcinogenic to humans”, respectively.

The NGOs assert that FDA need not conduct an independent assessment for any of the chemicals that are the subject of the FAP, as the Agency can rely solely on NTP and IARC reviews to conclude that the Section 172.525 clearances for the chemicals violate the Delaney Clause. Such rote reliance on these reviews would create a paradigm where FDA makes determinations about the carcinogenicity of a substance without ever looking at the studies and scientific information underlying its own determination. In support of this position, the FAP cites FDA's reliance on NTP reviews in evaluating the safety of certain tobacco products and, in some cases, food additive safety matters.⁹

In our opinion, the FAP mischaracterizes the reliance that FDA's Office of Food Additive Safety (OFAS) may place on NTP (or other) reviews. FDA has a statutory duty to conduct its own carcinogenicity and safety evaluations of food additives and, in doing so, must consider the weight of all the evidence concerning the carcinogenicity of the chemicals that are the subject of the FAP in reaching any conclusions regarding their legal status as regulated food additives.¹⁰ In addition to statutory concerns, automatic reliance on the reviews by other agencies, including non-U.S. entities, raises unlawful delegation questions.

Although OFAS may cite NTP (or other scientific body) reviews and studies in conducting its own carcinogenicity and safety evaluations, OFAS has always conducted its own independent evaluation of the potential for carcinogenicity and safety, which is consistent with the applicable

⁶ The FAP also cites evaluations conducted by California's Office of Health Hazard Assessment (OEHHA) for evidence that some of the chemicals that are the subject of the FAP are carcinogens.

⁷ NTP, Report on Carcinogens, Thirteenth Edition, Styrene, 2014. See <http://ntp.niehs.nih.gov/go/roc13>; NTP, Final Report on Carcinogens Background Document for Styrene, 2008. See <http://ntp.niehs.nih.gov/pubhealth/roc/listings/s/styrene/summary/index.html>.

⁸ IARC, Styrene, IARC Monograph – Volume 82-9, 2002, pp. 437-550. See <http://monographs.iarc.fr/ENG/Monographs/vol82/mono82-9.pdf>.

⁹ The FAP specifically cites an FDA warning letter issued to a company marketing *ginkgo biloba* leaf extract as an unapproved food additive. The Agency merely cited to an NTP study as evidence that the *ginkgo biloba* leaf extract is not Generally Recognized as Safe (GRAS) under its intended conditions of use. The Agency did not say the NTP study, in and of itself, was grounds for a determination that the substance is not GRAS. Specifically, the Agency noted that *reports* in the scientific literature appear to show *ginkgo biloba* to have a carcinogenic activity in animals.

¹⁰ See Section 409(c)(5) of the FD&C Act (codified at 21 U.S.C. § 348(c)(5)).

statutory criteria and accepted scientific practices.¹¹ Specifically, when evaluating the carcinogenicity of a substance, FDA may refer the matter to the Center for Food Safety and Applied Nutrition's Cancer Assessment Committee (CAC) or the Quantitative Risk Assessment Committee.¹² These assessments consider all scientific data available to the Agency using a weight of evidence approach.

Historically, OFAS has never relied solely on the results of an NTP or other review as a basis for concluding an additive is or is not a carcinogen. Indeed, FDA's credibility is predicated on it operating as an independent and science-driven organization.

III. Inherent limitations of third party reviews

A. The FDA and third-party review processes differ

Government agencies and other organizations conducting reviews create their individual processes, procedures and criteria based on foundational goals set forth in authorizing legislation, regulations or charters. Rarely, if ever, does the review process used by these other entities exactly align with FDA's statutory obligations and goals as well as agency policy and practices. We expand on this fact by focusing on NTP and IARC, as these are the two organizations cited by Petitioners.

The important differences between the review processes utilized by NTP and IRAC are exemplified by the inconsistent carcinogenicity classifications that these entities apply to the same chemicals. For example, IARC classifies acetamide (CAS Reg. No. 60-35-5), benzophenone (CAS Reg. No. 119-61-9) and ethyl acrylate (CAS Reg. No. 140-88-5) as "possibly carcinogenic to humans".¹³ However, NTP's 13th RoC does not contain any classifications for those chemicals. With this in mind, it is important for FDA to closely and independently review the basis and validity of all NTP or IARC classifications when relying on those classifications as part of a carcinogenicity evaluation.

B. Scientific evaluation criteria and agency science policies change

Science evolves and advances; it is a dynamic, not static, field. Generally accepted conclusions are subject to refinement and revision. For example, scientists continue to debate the health

¹¹ For example, when evaluating the safety of new food additives, OFAS does not merely review the information submitted as part of the food additive petition. Instead, OFAS conducts its own safety assessment and research to determine the safety of the proposed use.

¹² See FDA, Guidance for Industry and Other Stakeholders, Toxicological Principles for the Safety Assessment of Food Ingredients, Chapter II, Redbook 2000 (July 2000; Revised July 2007) (Redbook), available at: <http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/IngredientsAdditivesGRASPackaging/ucm2006826.htm>.

¹³ There are other examples of instances where IARC and NTP have adopted different carcinogenicity classifications for the same chemicals.

effects of various fats in the diet or, in emerging science, the view that ‘junk DNA’ is not superfluous, but serves necessary functions.

Even the process by which reviews and assessments are conducted change. In recent years, systematic review has become the benchmark for a number of agencies.¹⁴ For example, the U.S. Environmental Protection Agency (EPA) is adapting its procedures to be consistent with systematic review and evidence integration. Similarly, IARC now counts a single study using male and female animals as ‘two’ studies for purposes of assessing the sufficiency of the evidence. Moreover, NTP significantly changed its procedures before and after it issued the 12th RoC.

Best scientific practices evolve, sometimes against a background of scientific debate, suggestion, application and adjustment.¹⁵ As these practices evolve, the appropriate criteria relied upon to make judgments about particular types of studies also may change.¹⁶ Thus, NTP and IARC, as well as similar review organizations, are not an appropriate stand-alone basis for FDA regulatory action. Not only is new scientific information now available that these entities could not have relied upon, but NTP and IARC made conclusions against a backdrop of priorities and criteria that may be different from what FDA considers when it evaluates the carcinogenicity or safety of a particular substance. Close review and scientific scrutiny by FDA is essential to ensure the Agency maintains its independence and acts in accordance with the criteria and policies that provide for the protection of the public’s health and engender confidence from stakeholders in the Agency’s decision making process.

C. FDA must consider new studies since the NTP and IARC reviews were completed

Petitioners include references to studies completed after the NTP and IARC reviews as part of their submission. Thus, even the Petitioners tacitly recognize that FDA has an obligation to consider more recent studies. Notwithstanding this fact, the Petitioners ask FDA to simply accept their conclusion that no more recent study brings the NTP or IARC reviews into question. Of course, FDA is not free to do so, and no doubt that Petitioners would object to FDA simply accepting an industry characterization as correct without independent Agency analysis. We continue to maintain that the only acceptable approach is for FDA to independently evaluate all

¹⁴ Woodruff TJ, Sutton P. 2014. The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. *Environ Health Perspect* 122:1007–1014; <http://dx.doi.org/10.1289/ehp.1307175>.

¹⁵ Critical Reviews in Toxicology, October 2013, Vol. 43, No. 9 : Pages 753-784. L. Rhomberg, J. Goodman, et al, A survey of frameworks for best practices in weight-of-evidence analyses, *Critical Reviews in Toxicology*, vol. 43, No. 9 : Pages 753-784, October 2013.

¹⁶ K. Robert, K. Muris, et al. (2016): Criteria for Reporting and Evaluating Ecotoxicity Data (CRED): Comparison and perception of the Klimisch and CRED methods for evaluating reliability and relevance of ecotoxicity studies. *Environmental Sciences Europe* 2016, 28:7; DOI: 10.1186/s12302-016-0073-x available at: <http://www.enveurope.com/content/28/1/7>; see also, C.T.A. Moermond, R. Kase, et al. (2015) CRED: Criteria for Reporting and Evaluating ecotoxicity Data. *Environmental Toxicology and Chemistry* DOI: 10.1002/etc.3259

the relevant information before the Agency at the time of its assessment.¹⁷ New studies cannot be considered in isolation and need to be viewed within the broader context of other studies, that is, a systematic review and integration of information reflecting a weight of evidence assessment. We certainly believe that reviews by entities other than FDA can be helpful, and their consideration necessary to the ultimate assessment, but they are not dispositive.

D. The international health and safety community has moved away from rote reliance on IARC and NTP

Petitioners ignore a decades-long shift regarding the role of IARC and NTP assessments among health professionals. This is best exemplified by the Occupational Safety and Health Administration (OSHA) modifying its Hazard Communication Standard (HCS) to conform with the United Nations' (UN) Globally Harmonized System of Classification and Labeling of Chemicals (GHS). As explained below, in 2012, OSHA reversed three decades of automatically requiring employers to classify a substance as a carcinogen based on an NTP or IARC classification. Thus, these classifications are no longer considered a basis for automatic classification on Safety Data Sheets (SDS), formerly referred to as Material Safety Data Sheets (MSDS).

Prior to 2012, 29 C.F.R. § 1910.1200 (d)(4) of the federal HCS required manufacturers, importers, and employers to treat three sources as authoritative bodies for establishing that a chemical is a carcinogen. These sources were NTP's Annual RoC, IARC's Monographs, and the chemicals determined by OSHA to be carcinogens through substance-specific rulemakings and listings in 29 C.F.R. part 1910, subpart Z. This is no longer the case. Under HCS 2012, all requirements based on the NTP RoC and IARC Monographs have been eliminated. Instead, manufacturers and importers are required to "identify and consider the full range of available scientific literature and other evidence concerning the potential hazards",¹⁸ and then apply the applicable classification criteria in Appendix A to 29 C.F.R. § 1910.1200 under a weight of evidence analysis.¹⁹ OSHA explained the basis for the amendment as follows:

With the detailed criteria, and the weight of evidence approach in the GHS, OSHA indicated in the NPRM that it appeared to no longer be necessary to have such a floor or the one study rule.

¹⁷ For example, several new studies related to the carcinogenicity of styrene have been published in recent years that could rely on to reach a different conclusion than NTP or IARC. *See supra*, note 24.

¹⁸ 29 C.F.R. § 1910.1200(d)(2). Like the HCS, the GHS approach is based on a downstream flow of information from suppliers to users. 77 Fed. Reg. at 17,707.

¹⁹ 29 C.F.R. § 1910.1200, A.0.3 (Classification based on Weight of Evidence).

Thus, while Appendix A to 29 CFR § 1910.1200 “*allows* a manufacturer or employer to rely on the NTP designations for purposes of classifying chemicals,”²⁰ it is not mandatory and not determinative.

With this in mind, it is more than evident and consistent with international practice that NTP and IARC classifications do not make those substances carcinogens under the HCS. Further, an assessment as to carcinogenicity must be based on a weight of evidence approach. Adoption of this practice by OSHA, an Agency with a similar public health protection mandate to that of FDA, exemplifies the movement away from rote reliance on NTP and IARC reviews. The NTP and IARC reviews are not viewed as weight of evidence conclusions by the leading authorities in the international community, including OSHA, and it would therefore be incongruent for FDA to view them in this manner and rely on them as a singular basis for concluding that any chemical is a carcinogen or is not safe.

IV. An independent FDA assessment may differ from NTP’s conclusions

A. NTP was established for a fundamentally different reason than FDA

Many of the provisions in the Federal FD&C Act of 1938,²¹ as well as the Food Additive Amendments of 1958,²² exist to ensure the safety of food. The purpose of the NTP RoC was distinctly different. Its legislative origins were based on the allocation of cancer research efforts, a shift from prevention to treatment, and information to inform public behavior. Specifically, the legislative history teaches that the RoC was intended to guide cancer research, inform the public, and alert governmental agencies to potential regulatory issues.²³ None of this suggests that the NTP RoC was envisioned as an automatic basis for cancer classification or regulation by other federal agencies. Thus, it would be inappropriate for FDA to rely on the NTP RoC as a sole basis to conclude that a substance is a carcinogen or is otherwise not safe. Such a determination must be made on a weight of evidence basis that takes into consideration all of the available information about the substance.

²⁰ *Initial Statement of Reasons* at 9 (emphasis added).

²¹ Federal Food, Drug, and Cosmetic Act of 1938, Pub. L. No. 75-717, 52 Stat. 1040 (1938).

²² Food Additive Amendments of 1958, Pub. L. No. 85-929, 72 Stat. 1784 (1958).

²³ The concept of a comprehensive Annual Report for a list of carcinogens was first presented publicly at a 1978 Congressional hearing. See OFFICE OF TECHNOLOGY ASSESSMENT, U.S. CONGRESS, IDENTIFYING AND REGULATING CARCINOGENS 171 (U.S. Government Printing Office 1987), available at <http://www.princeton.edu/~ota/disk2/1987/8711/8711.PDF>. At the hearing, witnesses stressed a more preventive approach to tackling cancer that involved (1) more research on cancer-causing agents, and (2) dissemination of information to the public. H.R. REP. NO. 95-1192, at 17, 21 (1978).

B. FDA might reach a different conclusion on the human and animal evidence based on new data

New scientific studies and data are published constantly. As a result, the scientific literature on a given substance is subject to continuous updating. The release of this new information means the existing literature must be re-evaluated in light of the new information. For example, FDA might reach a different conclusion than NTP based on new or updated human, animal or other studies.²⁴ These studies were not available to NTP and, obviously, could not be considered. Therefore, new studies *could* be viewed by FDA as supporting the conclusion that a substance is *not* carcinogenic. Thus, it would be inappropriate for FDA to rely on prior NTP assessments now or in the future.

V. IARC itself warns that the Monographs are not the basis for governmental action

The Preamble to the IARC Monographs is clear that the Monographs are a starting place for government agencies, not a basis for regulation.²⁵

The Monographs are used by national and international authorities to make risk assessments, formulate decisions concerning preventive measures, provide effective cancer control programmes and decide among alternative options for public health decisions. The evaluations of IARC Working Groups are scientific, qualitative judgements on the evidence for or against carcinogenicity provided by the available data. These evaluations represent only one part of the body of information on which public health decisions may be based. Public health options vary from one situation to another and from country to country and relate to many factors, including different socioeconomic and national priorities. *Therefore, no recommendation is given with regard to regulation or legislation, which are the responsibility of individual governments or other international organizations.*²⁶

²⁴ See, e.g., Collins et al., (2013) Collins J, Bodner K, and Bus S, Cancer Mortality of Workers Exposed to Styrene in the U.S. Reinforced Plastics and Composite Industry, *Epidemiology* 24:2, 195-203; Coggon et al., (2014) Coggon D, Ntani G, Harris E, Palmer K, Risk of cancer in workers exposed to styrene at eight British companies making glass reinforced plastics, *Occup Environ Med* doi:10.1136/oemed-2014-102382; Ruder et al., (2014) 24th International Epidemiology in Occupational Health (EPICOH) Conference, "Challenges for Occupational Epidemiology in the 21st Century". 24-27 Jun 2014, Chicago, IL. The Ruder poster was published in *Occup Environ Med* 2014; v. 71, Suppl 1; pp A74-A75; doi:10.1136/oemed2014102362.232; Kolstad et al., (2014) 24th International Epidemiology in Occupational Health (EPICOH) Conference, "Challenges for Occupational Epidemiology in the 21st Century". 24-27 Jun 2014, Chicago, IL. *Occup Environ Med* 2014; v. 71, Suppl 1; pp A82-A83; doi:10.1136/oemed2014102362.257.

²⁵ "The Preamble to the IARC Monographs describes the objective and scope of the programme, the scientific principles and procedures used in developing a Monograph, the types of evidence considered and the scientific criteria that guide the evaluations. The Preamble should be consulted when reading a Monograph or list of evaluations." IARC, Preamble, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans (2006)(available at <http://monographs.iarc.fr/ENG/Preamble/index.php>).

²⁶ Preamble at 3 (italics supplied).

Moreover, the manner in which Working Groups implement the principles established by IARC may vary.

The Preamble is primarily a statement of scientific principles, rather than a specification of working procedures. The procedures through which a Working Group implements these principles are not specified in detail. They usually involve operations that have been established as being effective during previous *Monograph* meetings but remain, predominantly, the prerogative of each individual Working Group.²⁷

Thus, it is difficult, if not impossible, to ascertain how the general scientific principles in the Preamble are applied by each IARC Working Group.

Finally, the problem with stale reviews is evident when the dates of various IARC Monographs are considered. This is not a criticism of IARC, but merely reflection of the reality that IARC has limited resources to allocate. Thus, it would be inappropriate for FDA to blindly adopt IARC classifications as a basis for governmental action.

VI. A zero tolerance policy is infeasible for naturally occurring and fairly ubiquitous substances

The FAP claims that it is “appropriate – even necessary” for FDA to rely on the petition process to establish a zero tolerance so that companies do not claim that the seven substances are safe for use as flavoring agents in food. Such a statement belies a fundamental misunderstanding of the ubiquitous nature of certain substances. It would be impractical for FDA to establish a zero tolerance for a substance in food when it is a naturally occurring constituent of our environment.

For example, naturally occurring styrene was first extracted from the oriental sweetgum tree (also called levant styrax, after which styrene is named). Styrene also occurs in the similarly named, but unrelated, styrax tree. The primary sources of exposure to styrene in air appear to be industrial activities and internal combustion engine exhaust, with estimates that overall ambient air exposures to styrene typically range around 0.001 ppm (= 1ppb = 0.0043 mg/m³). Styrene occurs naturally in some foods, including strawberries, wheat, peanuts, beef, and spices, such as cinnamon. It is naturally produced as a metabolite in the processes of making some foods, including wine, beer, grains, and cheeses.

The natural occurrence of many of these chemicals in the environment makes a zero tolerance policy infeasible. It would also detract from and interfere with FDA’s other broad statutory mandates that are in place to assure a safe food supply. These include the GMP and adulteration provisions of the FD & C Act and its implementing regulations, including the recently added provisions from the Food Safety Modernization Act.²⁸ For these reasons, a zero tolerance policy for these chemicals is inappropriate.

²⁷ Preamble at 1-2.

²⁸ Food Safety Modernization Act, Pub. L. No. 111-353, 124 Stat 3885 (codified in scattered sections of 21 U.S.C.).

VII. FDA should continue its rational application of the Delaney Clause

The FAP requests that FDA interpret the Delaney Clause as a legal standard that imposes a “bright line” for determining which food additive are safe. For many scientific, legal, and policy reasons, FDA has always interpreted the Delaney Clause in a more practical and nuanced fashion. Specifically, FDA developed the so-called “Constituents Policy” as a means of dealing rationally with food additives that clearly present no meaningful toxicological risk, but that may contain minute levels of carcinogenic impurities or carcinogenic residual starting materials (*e.g.*, carcinogenic monomers used to make polymers).²⁹ Under the Constituents Policy, FDA distinguishes between an additive as a whole and its constituents. If an additive as a whole is not carcinogenic, the presence of unavoidable low levels of carcinogenic constituents does not automatically trigger the Delaney Clause, barring the use of the additive. Instead, the safety of the additive may be evaluated under the general safety provisions of the Act.³⁰ The use of the Constituents Policy as a means of rationally interpreting the Delaney Clause where appropriate has been judicially upheld.³¹

Adoption of the Constituents Policy by FDA constitutes recognition by the Agency that substances cannot be produced to an unascertainable standard (*i.e.*, one in which all infinitesimal impurity exposures that have no impact on the public health are eliminated). With this in mind, it is critical for FDA to continue its rational interpretation of the Delaney Clause. Failure to do so could result in the revocation of hundreds of clearances for safe additives, would spark significant public confusion, would represent the abandonment of a long-standing Agency practice that functions as a bedrock principal in the realm of food additive regulation, and would in no way benefit public health or safety.

VIII. Conclusion

As demonstrated in these comments, the FAP should be denied. Although SIRC supports removal of styrene from the flavorants regulation based solely on abandonment (which is the subject of a separate filing), SIRC, GMA, IFAC, and SPI oppose FDA delisting any substance based on classifications in the NTP Report on Carcinogens or the IARC Monograph. Any

²⁹ See 47 Fed. Reg. 14,464 (Apr. 2, 1982). In a November 26, 2004 Federal Register notice (69 Fed. Reg. 68831, 68836), FDA withdrew this advance notice of proposed rulemaking (ANPR) along with approximately 80 other proposed actions and rules that were no longer considered viable candidates for final action. The withdrawal represents an effort by the Agency to reduce its regulatory backlog and focus its resources on current public health issues. The notice states that, “withdrawal of a proposal is not intended to affect whatever utility the preamble statements may currently have as indications of FDA’s position on a matter at the time the proposal was published,” and further that, “in some cases the preambles of these proposals may still reflect the current position of FDA on the matter addressed.” Thus, despite the Agency’s withdrawal of the ANPR, the Constituents Policy outlined in the April 2, 1982 Federal Register notice remains a valid policy by which to evaluate minor carcinogenic constituents of food additives.

³⁰ The carcinogenic risk due to exposure to the constituent is determined using a statistical risk assessment procedure based upon potential exposure and such toxicological data as are available.

³¹ *Scott v. FDA*, 728 F.2d 322 (6th Cir. 1984).

substantive and involuntary delisting must rest on a thorough and independent FDA assessment. In addition, FDA should not adopt a zero tolerance policy, particularly for substances that are naturally occurring in food and food products.

For these reasons, the Petition should be denied.

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