Environmental Science & Technology

Policy Analysis

pubs.acs.org/est

Can Chemical Class Approaches Replace Chemical-by-Chemical Strategies? Lessons from Recent U.S. FDA Regulatory Action on Per- And Polyfluoroalkyl Substances

Alissa Cordner*

Whitman College, Department of Sociology, 345 Boyer Ave., Walla Walla, Washington 99362, United States

Lauren Richter

Northeastern University, Department of Sociology and Anthropology, Boston, Massachusetts 02115, United States

Phil Brown

Northeastern University, Department of Sociology and Anthropology, and Department of Health Sciences, Boston, Massachusetts 02115, United States

ABSTRACT: Concern about the toxicity and exposure of per- and polyfluoroalkyl substances (PFASs) is growing among scientists, regulators, and residents of contaminated communities. In 2016, the United States Food and Drug Administration (FDA) removed three food contact substances (FCSs) containing perfluorinated chemicals from the list of approved FCSs due to concerns regarding chemical safety. To investigate the significance and limitations of the FDA's regulatory action for environmental health research, advocacy, and regulation, we conducted a media analysis and qualitative interviews with a range of involved stakeholders. We find that the FDA's regulatory action represents a potential shift from chemical-by-chemical regulation toward class-based regulation, where groups of chemicals can be identified as sharing properties and risks, and are thus evaluated and regulated together. The FDA decision sets an important precedent of using a petition process to delist chemicals based on a safety standard. However, the narrow reach of this action also highlights the need for more comprehensive, precautionary chemical regulation capable of thoroughly evaluating classes of chemicals, and raises important questions about how classes of chemicals are delimited in environmental health science and regulation.

INTRODUCTION

On January 4, 2016, the United States Food and Drug Administration (FDA) removed three food contact substances containing long-chain per- and polyfluoroalkyl substances (PFASs) from the list of approved food contact substances.[1] This action effectively banned the uses of three subclasses of chemicals based on structural similarity to other persistent, toxic, and bioaccumulative PFASs. (We refer to all PFASs as a "class" of chemicals, and more delimited groups of PFASs as "sub-classes" of a broader class). FDA's regulatory action potentially represents a shift from chemical-by-chemical regulation toward class-based chemical regulation, where groups of chemicals are identified as sharing properties and assessed risks, and are thus regulated together. But is this action part of a broader shift on the part of regulatory agencies toward more comprehensive chemical management, or an isolated and symbolic change with little potential to impact public health? Our analysis draws on a review of recent media coverage and in-depth interviews with scientists, state and federal regulators, industry representatives, and advocates working for environmental and health nonprofits. We evaluate a range of contested meanings attributed to the recent FDA decision to examine the significance of chemical class-based approaches to chemical monitoring and regulation.

U.S. Chemical Regulation. In the United States, chemicals are regulated by multiple agencies based on their uses. Most industrial uses of PFASs are overseen by the Environmental Protection Agency's (EPA) Toxic Substances Control Act (TSCA), while their use in food contact materials is governed by the FDA. Regulatory agencies make decisions about chemical safety in the face of incomplete and uncertain scientific evidence. The vast majority of the more than 84 000 industrial chemicals registered with the EPA lack any data on

Received: September 30, 2016
Revised: November 4, 2016
Accepted: November 7, 2016
Published: November 7, 2016

DOI: 10.1021/acs.est.6b04980
Environ. Sci. Technol. 2016, 50, 12584−12591

how people are exposed to them, at what levels, and with what consequences.[2−4] Significant limitations in the original 1976 bill and the TSCA reform bill passed and signed into law in June of 2016 mean that regulation of most chemicals, especially those that were registered as existing substances before the original bill was enacted, is inadequate.[5−7] Although the reformed TSCA has greater authority to evaluate new and existing chemicals and to require chemical manufacturers and users to develop exposure and toxicity data, it requires evaluation of only 20 high-priority chemicals at a time, limits states' ability to take regulatory action on chemicals under review, and leaves the EPA unable to assess potential cumulative and synergistic effects of chemicals in commerce.[8]

Regulation of newly developed and existing chemicals primarily occurs on a chemical-by-chemical or use-by-use basis.[5] Laboratory advances in high throughput screening, computational toxicology, and structure−activity relationship modeling are increasing scientists' abilities to understand how chemical similarities may function across chemical classes. The EPA conducts extensive structure−activity relationship modeling using chemical analogs to evaluate the potential exposure and toxicity concerns for new chemicals submitted for premanufacture review and approval.[9] However, limited precedent exists for regulating classes of chemicals. The original TSCA banned the manufacture, processing, use, and distribution of all polychlorinated biphenyls (PCBs), and the Montreal Protocol's chemical restrictions to reduce the use of ozone-depleting substances grouped several chlorofluorocarbons into a chemical class. Generally, however, regulatory responses for existing chemicals address one chemical and one use at a time.

PFASs. PFASs are a broad class of human-made compounds that contain chains of carbon and fluorine atoms, more specifically "aliphatic substances containing one or more C atoms on which all the H substituents present in the nonfluorinated analogues from which they are notionally derived have been replaced by F atoms."[10] (While these compounds have sometimes been referred to as "perfluorinated chemicals" or PFCs, this is outdated and confusing terminology.)[11] They provide stain, grease, and water resistance in the aerospace, automotive, building, construction, and electronics industries, and in common consumer products such as dental floss and microwave popcorn bags; they are also used in numerous industrial and commercial processes and in aqueous film-forming firefighting foams.[11,12] Because of PFASs' broad use in consumer products, environmental mobility, and presence in numerous contaminated sites around the country, exposure to the general public is ubiquitous. The 2009 NHANES report by the Centers for Disease Control measured 12 PFASs in a nationally representative sample of 2500 U.S. residents, and found four PFASs in the serum of nearly all the people tested.[13,14]

Over the past decade, scientific research on PFASs has grown rapidly, from fewer than 300 published studies before 2000 to over 3000 studies by 2015.[15] Most research and regulation has focused on "long-chain" PFASs, perfluoroalkyl carboxylic acids with carbon chain lengths of C8 or higher, and perfluoroalkanesulfonates with carbon chain lengths of C6 or greater.[16] The greatest attention has focused on perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), which were widely used in manufacturing and industrial processes in the United States until the early 2000s. In the United States, PFOS manufacturing was phased-out by 3M by 2002, and the EPA directed a voluntary PFOA-stewardship program to work toward elimination of PFOA and related long-chain PFASs.[17] The EPA recently established nationwide drinking water health advisory levels for PFOA and PFOS in drinking water of a combined 70 parts per trillion.[18] Some long-chain PFASs have also been regulated internationally: for example, PFOS was added to the Stockholm Convention on Persistent Organic Pollutants in 2009, and Canada prohibited the manufacture, use, sale, and import of certain long-chain PFASs in 2016.[19,20]

Though the EPA's current drinking water advisory levels are lower than levels used in animal toxicology studies or documented in contaminated communities, population-level exposure is concerning because substances in this chemical class demonstrate the potential for hormone disrupting effects and bioaccumulation, and some PFASs do not degrade rapidly or at all in the environment.[21] Epidemiological research has linked human exposure to PFOA with high cholesterol, ulcerative colitis, thyroid disease, testicular and kidney cancers, reproductive and developmental toxicity, and pregnancy-induced hypertension.[22,23] Thousands of individuals with these health outcomes residing in contaminated portions of Ohio and West Virginia are currently suing DuPont for personal injury compensation.[24] Additional suspected health impacts of exposure to certain PFASs include endocrine disruption, obesity, reproductive problems, birth defects, various cancers, stroke, and developmental problems in children.[15]

FDA Food Additives Regulation. The U.S. FDA regulates PFASs under their food additives authority. This authority includes both ingredients added to food and indirect food additives, substances that become part of the food when they migrate from food packaging materials, facilities where the food was manufactured, or other points on the production chain.[25,26] Two publicly available lists are central to understanding the FDA's management of food additives: Title 21 of the *Code of Federal Regulations* (CFR) and the *Food Contact Notification* (FCN) list.[26,27] The FDA's standard for safety for the CFR and FCN list requires a conclusion that there is "reasonable certainty of no harm" from exposure from a chemical use.[28] Manufacturers of food contact substances petition the FDA to approve new food additives. If approved, the FDA publishes the change to the CFR in the Federal Register and accepts comments on the decision. A manufacturer, whether manufacturing chemicals or products using those chemicals, may legally use any substance listed in the CFR, and chemicals are rarely removed from the CFR list once approved.

Today the FCN list has largely replaced the use of the CFR list for new food contact substances. The FDA Modernization Act of 1997 supplemented the previous food additive petition process with a requirement that manufacturers submit a premarket notification to the FDA for review. If the FDA approves the notification or fails to respond within 120 days of the notification, the FDA posts these substances to the FCN list.[29] These publicly listed notifications are manufacturer-specific, and exact amounts and production processes remain confidential. For example, a food contact paper manufacturer could purchase a specific substance listed on the FCN directly from the food additive manufacturer. In essence, the CFR lists chemicals that can be used by any manufacturer, while the FCN lists chemicals produced by particular manufacturers.

■ DATA AND METHODS

This study is part of a larger project on the social and scientific discovery of PFASs, which received Institutional Review Board

DOI: 10.1021/acs.est.6b04980
Environ. Sci. Technol. 2016, 50, 12584−12591

approval from Northeastern University. (This larger project involves interviews, media and content analysis, and observational research at federal regulatory offices, community meetings in contaminated regions, scientific conferences on PFASs, and public hearings by state and local agencies regarding water contamination in multiple states.) We conducted in-depth qualitative interviews with 51 stakeholders, including academic and regulatory scientists (11), state and federal regulators (12), scientists and organizers working with nongovernmental advocacy organizations (11), industry and supply chain representatives (3), residents of contaminated communities, lawyers, and journalists (14). For this paper we draw directly on interviews with advocates and regulators involved with the FDA's action on PFASs, though our analysis is informed by interview data from the full project. Respondents were identified through their public work on PFASs and by referral from other respondents and informants. Interviews were semistructured, and covered the following themes: respondents' personal and professional trajectories, their work on PFASs, the social and scientific discovery of PFASs, regulation of PFASs and other emerging contaminants, awareness of PFAS contamination, advocacy and litigation related to PFASs, and anticipated future work on PFASs. Interviews lasted from 30 to 120 min. Interviews were conducted in-person or over the phone, and were digitally recorded and transcribed. Respondents had the option to be named or be referred to anonymously. Because some of the respondents quoted in this paper requested anonymity, we chose to not identify any individual respondents by name and instead to refer to individuals by general professional categories. All descriptions of interviewees' responses or perspectives come from our interviews; all quotes without external references are verbatim quotations from our interviews.

Further data come from a media analysis of coverage of the FDA decision. Media articles were gathered from Google Alerts that collected news stories about PFASs as they were published on the web, and from a LexisNexis (Academic Universe) search for articles from 2016 containing the terms "FDA perfluorinated", "FDA PFAS", and "FDA PFC". Interview transcripts and media articles were analyzed through multiple readings by the authors to identify and code for themes.

RESULTS

FDA Petition Process and Decision. Prior to the FDA's action on these three groups of PFASs, the agency had not considered classes of chemicals in their treatment of FCSs (FDA documents often use the terminology "PFCs" to refer to this class of chemicals; we follow their language only when using direct quotations). The FDA precedent for removing chemicals from CFR or FCN lists is extremely rare. Based on interviews with government officials, we identified only two instances prior to the agency's action on PFASs in which compounds were delisted by the FDA. First, in 2015 the FDA determined that partially hydrogenated oils (trans fats) no longer met "Generally Recognized as Safe" (GRAS) criteria based on identified human health risks.[30] This represented a rare example of the FDA removing a product from the CFR list. In the second instance, Bisphenol-A (BPA) was removed from the CFR list following external petitions from nonindustry stakeholders, but in this case the FDA justified its decision based on "market abandonment" rather than safety.[31,32] In 2012 and 2013, a pair of petitions by the American Chemistry Council and Congressman Edward Markey stated that manufacturers were no longer using BPA to produce polycarbonate resins or epoxy-based resins for baby bottles, spill-proof cups, or infant formula packaging, and therefore the uses should be removed from the FDA's food additive list based on market abandonment. The FDA made clear that this decision was not based on their evaluation of BPA's safety: "an amendment of the food additive regulations based on abandonment is *not* based on safety."[33] However, the use of this petition process to remove chemicals from the list of allowed food additives rather than add chemicals (the more typical use) was significant.

Following EPA-negotiated phase-outs of PFOA and PFOS in the mid-2000s, the FDA conducted several toxicological evaluations of PFASs. In 2007, the FDA determined that PFOA is a carcinogen, and that carcinogenicity is a concern for structurally similar long-chain PFASs.[23] In 2010, the FDA completed a toxicological review of long-chain PFASs, focusing on PFOA's potential for reproductive and developmental toxicity.[23] The FDA review concluded that significant toxicity concerns existed for long-chain PFASs generally and that the association between increased biopersistence and longer chain length supported a generalization "to the entire class" of "long-chain perfluoroalkyl substances".[23] Consequently, the FDA worked with U.S. manufacturers on a voluntary agreement to stop using those compounds in food contact materials.[34] Major companies committed to no longer manufacture or distribute FCSs made with these compounds, though a government representative told us that the Agency conducted no monitoring or testing to verify market abandonment. Furthermore, three subclasses of long-chain PFASs remained on the CFR list,[35] and thus their use technically remained legal.

Motivated by these events, environmental advocates led by the Natural Resources Defense Council (NRDC) decided to petition the FDA to remove three subclasses of long-chain perfluoroalkyl substances and all precursor chemicals that can degrade into this set of compounds, from the CFR list of chemicals approved for use in food contact materials: "Diethanolamine salts of mono- and bis(1*H*,1*H*,2*H*,2*H* perfluoroalkyl) phosphates where the alkyl group is even-numbered in the range C8−C18 and the salts have a fluorine content of 52.4 percent to 54.4 percent as determined on a solids basis," originally registered by DuPont in 1967; "Pentanoic acid, 4,4-bis [(*gamma-omega*-perfluoro-C8−20-alkyl)thio] derivatives, compounds with diethanolamine", registered by Ciba-Geigy in 1983; and "Perfluoroalkyl substituted phosphate ester acids, ammonium salts formed by the reaction of 2,2-bis[([gamma], [omega]-perfluoro C4−20 alkylthio) methyl]-1,3- propanediol, polyphosphoric acid and ammonium hydroxide", registered by Ciba-Geigy in 1996 and 1997.[35] All three of the FCSs named in the petition contain extended alkyl chains where all of the hydrogens are replaced by fluorine (hence the FCSs are "perfluorinated).

This petition was based on a "safety standard" requiring the FDA to conclude that there was no longer "reasonable certainty of no harm" from exposure from a chemical use. In prepetition discussions with FDA representatives, the petitioners learned of the agency's 2010 toxicological review of long-chain PFASs. In the words of one respondent involved in the petition process, a constellation of factors inspired them to pursue the petition: FDA's efforts to establish the voluntary agreement with PFASs manufacturers "told us that they... saw them [long-chain PFASs] as a problem," and the market abandonment BPA petitions demonstrated that it was possible to use "the food

DOI: 10.1021/acs.est.6b04980
Environ. Sci. Technol. 2016, 50, 12584−12591

additive petition to do a removal" of compounds from the CFR list of approved substances.

The petition was spearheaded by the NRDC, with an additional eight cosigning organizations: Breast Cancer Fund, Center for Environmental Health, Center for Food Safety, Center for Science in the Public Interest, Children's Environmental Health Network, Clean Water Action, Environmental Working Group, and Improving Kids' Environment. Additionally, the petitioners shared the petition with industry colleagues. "We tell the industry every step of the way," one advocate noted, arguing that this benefits the process because chemical users and manufacturers "know these chemicals better than we do."

Respondents from both the FDA and the petitioning nongovernmental organizations (NGOs) described the process as "iterative" and a "back-and-forth" between petitioners and the FDA. After an initial prenotice consultation in 2014, NRDC submitted two draft petitions, which were reviewed and commented upon by FDA representatives. FDA scientists provided feedback on the language and arguments in the petition, and asked for "more rigor" in the petition, specifically requesting that the petitioners update the agency's 2010 toxicological review of long-chain PFASs' potential for reproductive and developmental toxicity.

The final petition submitted on July 27, 2015 requested that the CFR be amended "to no longer provide for the use of three categories of perfluorinated FCSs" based on toxicological evidence suggesting that the compounds "raise safety concerns for dietary exposure," and that therefore "the authorized uses of these FCSs no longer meet the safety standard of 'reasonable certainty of no harm.'"[36] In accordance with the FDA's own toxicological review, the petitioners used a "structural class-based argument" that grouped together all long-chain perfluorinated compounds because of structural similarities, concerns about biopersistence, evidence of biotransformation of some longer-chain PFASs into PFOA, and reproductive and developmental toxicity concerns of certain long-chain PFASs. NRDC presented the results of an updated literature review on PFOA's adverse developmental effects, supporting FDA's 2010 conclusion, and also pointed to the EPA's recent Significant New Use Rule (SNUR) for long-chain PFASs, arguing that "EPA's actions constitute further evidence of a consensus between regulatory agencies that significant safety concerns exist for long-chain PFCs as a class."[37] In response, the FDA concluded that "the available evidence raises significant questions as to the safety of the authorized FCSs."[1] FDA review teams recalculated migration and updated exposure estimates for the three PFAS subclasses, concluding that "these exposure estimates may not be accurate and may not reliably represent consumer exposure."[36]

In response to the petition, the Society of the Plastics Industry (SPI), a trade association representing fluoropolymer manufacturers, wrote to the FDA that the three PFASs "represent an old technology that has since been replaced by alternative materials" and were no longer manufactured.[38] On this basis, SPI concluded that the PFASs "should be removed from 21 C.F.R. § 76.170 on the basis of abandonment."[38] Nine companies confirmed that they were not manufacturing, importing, or maintaining inventory of the materials identified in the petition, and did not intend to manufacture or import them in the future, signaling market abandonment.[39]

Although the industry's set of comments explicitly favored a market abandonment argument, the FDA instead acted upon the safety standard argument. The FDA published its final decision on January 4, 2016, confirming that the three subclasses of PFASs were being removed from the food additives list for safety concerns, following the agency's definition of safety as "a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended condition of use".[1] They reaffirmed their determination that it was appropriate to treat long-chain perfluoalkyl compounds "on a general basis" and concluded that accumulated evidence related to PFOA's toxicity could be applied to other long-chain PFASs.[1] Amendments to the approved food additives list become final rules upon their announcement in the Federal Register, with a 30-day window for objections, and so the January 2016 rule became final.

The FDA's action received little coverage in traditional media, with only eight relevant sources appearing in the online database LexisNexis. Two Internet and newswire services, Progressive Media and PMS Plus Media Solutions, published articles on the FDA actions and its consequences for industry research and development. The only article that appears to have actually been published in print media was from the *Daily Record and Sunday Mail*, a Scottish tabloid, with the eye catching headline, "Munchie Box Scandal" (a munchy or munchie box is a slang Scottish term for a takeaway food container).[40] LexisNexis also archived press releases from the Institute of Food Technologists describing the FDA decision, and from American Forest & Paper Association critiquing "news reports" of the decision for "creating undue worry and giving a bad rap" to pizza boxes, when "U.S.-based manufacturers stopped using these agents in pizza boxes over four years ago".[41]

The decision was generally interpreted in the media and by some NGOs as a "ban" on all PFASs in food packaging. Headlines such as "Authorities in the U.S. have banned chemicals used in pizza boxes because of a link to cancer" inaccurately suggested that PFOA or all PFASs had been affected by the FDA's action.[40] In fact, the FDA's action was limited in scope to only three sets of FCSs containing long-chain PFASs that were no longer being used or manufactured in the U.S.

Implications of the FDA Decision. Despite the narrow focus of the FDA action on these compounds, it establishes precedent in two important ways. First, in treating long-chain perfluoralkyl compounds as a class and using the known risks of PFOA to anticipate risks of other long-chain PFASs, it confirms FDA's ability to regulate chemical classes or subclasses rather than individual chemicals. As an NRDC leader explained, "it's the first time they [FDA] have designated a class of chemicals to be a problem. So they basically said long-chain... perfluorinated compounds are a class.... It's an extraordinary decision because it says, if there's no data, we're going to assign to the chemical the hazard we see showing up for the well-studied chemicals in the class." Similarly, an advocate with the Breast Cancer Fund said "the fact that they are willing to look at the toxicity data of similarly situated substances is important" because it moves beyond chemical-by-chemical regulation.

Second, the FDA's action establishes that the petition process can be used to remove chemicals from FDA-approved lists on the basis of a safety standard. An FDA representative confirmed that this was, to his knowledge, "the first time that the food additive petition has been used to revoke or de-list the use of a food additive based on a safety argument," though he noted that FDA has previously revised its regulations based on

DOI: 10.1021/acs.est.6b04980
Environ. Sci. Technol. 2016, 50, 12584−12591

safety concerns "on its own," outside the petition process. An advocate involved in the petition process noted that this provides hope to NGOs that future petitions based on a safety standard will be successful.

Additionally, the FDA's action points to the potential for cross-regulatory alignment. Chemical regulation in the U.S. is generally siloed by use: multiple offices or agencies potentially regulate the same compounds for industrial, food, pharmaceutical, agricultural, and military uses. As one official noted, "interagency coordination is something that we have pushed for... because there's so many different agencies that regulate different exposures of the same chemicals." The NRDC petition emphasized the EPA's SNUR of these long-chain PFASs as evidence in support of the FDA's petition. Establishing chemical risk in one government agency can support other agencies taking comparable or related action. It also pressures manufacturers, setting a precedent that their products are dangerous enough to warrant regulatory action. This action may also impact global commodity chains that include the use of long-chain PFASs for FCSs for import to the U.S.

However, the FDA's regulatory action has limited impact on companies use of or individuals' exposure to PFASs more broadly. The action did not restrict other PFASs beyond the three subclasses removed from the CFR, and it also did not address other common uses of PFASs, including personal care products and industrial applications, or common routes of exposure to PFASs, such as contaminated drinking water and consumer goods. Furthermore, the FDA has limited enforcement capacity related to this decision. An FDA representative explained that the onus in complying with the food additives regulation lies on the manufacturers and the Agency has no plans to test imported goods for the presence of the delisted PFASs, citing lack of resources.

As a result, some described the FDA's action as a symbolic victory. In an online statement, the Environmental Working Group (EWG), a copetitioner, called the FDA's actions "belated" and "too little and too late," occurring ten years after activists called attention to the issue and five years after companies stopped producing the compounds.[42] The EWG's statement further argued that the decision "does nothing to prevent food processors and packagers from using almost 100 related chemicals that may also be hazardous."

The decision also reveals the limitations of what advocates call "whack-a-mole" chemical substitution. As with other emerging contaminants like BPA and types of flame retardants, regulating chemicals of concern does not mean that replacement chemicals will have improved exposure or toxicity profiles.[43,44] Additionally, in the case of this FDA decision, regulatory action has been applied to uses of chemicals that are no longer occurring, revealing similarities with other regulatory backstops including the EPA's "dead chemical SNUR" process that precludes future uses of restricted chemicals, or state-level bans of individual chemicals beyond known uses to prevent market expansion.

An additional limitation is that petitions take a significant amount of nonprofit organizations' time and resources. As an advocate explained, "it's a lot of work to write these petitions.... You write it and you go to the FDA and they say, 'well, that's not quite what we need, this is what we need'. So it's like this iterative process with FDA." This same advocate praised the FDA for taking the process seriously: "We feel that FDA approaches it with seriousness. They put time in on these, they do a good job, they ask reasonable questions. So far we've been impressed".

With both benefits and drawbacks, the petition process is unique and opens up potential for further environmental regulation. Although stakeholders view the process as valuable and productive, the substantial amount of time and expertise required to submit a successful petition raises questions about whether petitioning will become a widespread advocacy strategy. Additional petitions submitted by NRDC and collaborating organizations, addressing perchlorate in food containers and synthetic flavors as food additives, remain under review by the FDA. In March 2016, after the FDA exceeded its required six-month review timeline for the perchlorate petition by nine months, the petitioners sued FDA to force action.[45] A third petition to remove a broad subclass of ortho-phthalates from FDA approval as food additives and in FCSs was published in the Federal Register in May 2016.[46]

DISCUSSION AND CONCLUSION

Regulation of environmental risks has been characterized as ranging from a precautionary approach, in which protective action is taken in the face of uncertainty, to a reactive approach, in which conclusive evidence of documented harm is required before taking action.[47−49] The reactive approach currently predominant in the United States means that chemicals of concern often remain in use for decades after initial concerns about health impacts emerge. For example, despite widespread consensus regarding the neurotoxic effects of lead, its use in aviation fuel, ammunition, and some industrial processes remains legal in the United States.[50,51] Though public health advocates, environmental health NGOs, and some regulators consistently push for more precautionary regulation, industry representatives often exert significant influence on regulation through direct lobbying and the "revolving door" that moves influential individuals between public and private sector employment.[52,53] Historians and sociologists of science have demonstrated that tobacco, fossil fuel, and chemical industries have taken advantage of reactive regulatory systems to keep hazardous products in commerce by concealing evidence, using supposedly independent groups to influence public opinion, calling for additional but irrelevant or unnecessary scientific exploration, or gathering cohorts of paid experts to cultivate public uncertainty about the health impacts of their products.[54−56]

The FDA's decision on certain PFASs complicates matters since it does not follow simple dichotomy between reactive and precautionary regulation. On the one hand, it provides a clear example of reactive regulation of a compound no longer believed to be in use, justified by a significant amount of toxicological and epidemiological evidence. On the other hand, it represents a potential shift toward precautionary regulation because the FDA took action before extensive and concrete data existed on each chemical under consideration; instead, the safety determination was made on the basis of other chemicals in the class, not the specific compounds under consideration. It also represents a departure from industry influence, since the petition came from NGOs, and the FDA declined to decide in accordance with industry's preferred abandonment interpretation.

The FDA decision must be understood in the context of other recent class-based actions on PFASs. In March 2015, Biomonitoring California, the only state biomonitoring program in the United States, expanded their program to

DOI: 10.1021/acs.est.6b04980
Environ. Sci. Technol. 2016, 50, 12584−12591

include PFASs as a class.[57] This is significant because government biomonitoring has played a major role in scientific and public awareness of the extent of chemical presence in human bodies. The National Health and Nutrition Examination Survey (NHANES), the national biomonitoring project, analyzed 12 PFASs for its 2009 Fourth Report. Biomonitoring California's subsequent addition was based on their authority to test any compounds on the NHANES list. From that testing and their knowledge of the broader scientific literature, members of Biomonitoring California's Scientific Guidance Panel were aware that the phase-out of long-chain PFASs "led to the development of a large number of replacement PFASs,"[57] and potentially higher uses of less-effective replacement compounds. This led them to add 20 specific PFASs to the testing list and "the entire class of PFASs to the list of designated chemicals."[57] As Biomonitoring California describes, "Listing of this broad group would give the Program the flexibility to choose new PFASs of potential health concern that would be appropriate to measure in response to market shifts."[57] Though they are unable to test for all PFASs at this time, the assumption is that the class as a whole is deserving of monitoring. Using a semi-nontargeted analysis, they will learn more about which compounds to include in future testing.

Another key element is increased media attention, public awareness, and litigation. Media coverage can influence the spectrum of possible regulatory outcomes in multiple ways: by furthering a certain social construction of how environmental problems are understood, framing issues and solutions in particular ways, increasing public awareness and concern about an issue, or presenting stakeholders as more or less favorable.[58−60] Numerous journalist stories have accompanied recent discoveries of PFOA and PFOS contamination linked to industry-related contamination in Bennington, VT and Hoosick Falls, NY, and to firefighting foam-related contamination in Portsmouth, NH and Colorado Springs, CO. PFOA contamination has also been discovered in Flint, MI, a city already suffering from massive lead contamination. Recent attention to long-term litigation against chemical manufacturers DuPont and 3M has added to the convergence of events around PFASs.[61] Further, a recent editorial in *Science* notes decisions by major manufacturers and retailers to phase out the use of PFASs broadly.[62]

The FDA's action also reflects a shift to multisector activism and multiactor governance.[63] While past understandings of environmental governance emphasized separate roles of the state, market, and civil society, contemporary research highlights hybrid and multiscalar modes of governance involving a range of state, market, and nongovernmental players.[64,65] The use of the FDA petition process also represents a novel strategy on the part of NGOs. Social movement scholars increasingly recognize that power may be dispersed across various institutions, and that NGOs engage in "multi-institutional politics" that target a variety of state and nonstate institutions.[66]

The FDA decision has public health significance for two reasons. First, the impetus behind the FDA's actions came from the environmental advocacy sector, unlike most historic FDA actions that were motivated by industry suggestions or internal governmental activity. For example, FDA acted on BPA because of industry's self-identified market abandonment, and thus far has failed to regulate BPA more broadly. This reveals similarities with how regulation of flame retardant chemicals has been motivated by voluntary industry phase-outs and state regulations supported by environmental and health advocates.[43]

Second, the FDA action buttresses the legitimacy and reach of arguments that chemicals with closely similar structures can be assessed as a class in the absence of data on individual chemicals' exposure and toxicity profiles, or when chemicals in a class can be transformed into known chemicals of concern. This attention to chemical classes and degradation products echoes the "Madrid Statement," a consensus document regarding exposure and toxicity concerns about PFASs developed by an international network of scientists.[67] Under such programs, the chosen definition of a chemical class is important. The PFOA Stewardship Program, for example, includes only PFOA, PFOA-precursors, and longer-chain chemical homologues; as a result, numerous short-chain PFASs have been introduced to the market or are now being produced in greater volumes. Without adequate evidence that replacement chemicals are truly safer, a narrowly defined chemical class may not be adequately protective of public health.

The case of PFASs highlights the need for attention to what we term the full "regulatory lifecycle" of regulation development, passage, implementation, and ongoing maintenance. Policy scholars have noted that governments influence regulatory processes and private sector initiatives (such as voluntary industry standards) through various mechanisms at multiple stages, including agenda-setting, rule formation, implementation, monitoring, enforcement, and evaluation.[68,69] Environmental regulations and policies have the potential to impact public and environmental health not only in how they are originally written, revised, and passed, but in how they are implemented and what resources are devoted to monitoring and enforcement. This case also demonstrates that regulatory programs must be able to rigorously encompass additional chemicals of concern. The FDA's petition process to remove (or add) chemicals to the CFR is time-consuming and resource-intensive, though the Agency can remove chemicals from approved lists without waiting for an external petition or asking for manufacturers' voluntary engagement. A streamlined petition process would be beneficial to those concerned with chemical safety and health concerns.

Regulatory activity in one government location can have broader impact on other governmental agencies and offices. Greater coordination is needed between the FDA and other agencies responsible for managing areas of chemical safety, including the EPA and Department of Defense. This could be supported through Presidential executive order or Congressional mandate, and technical knowledge and capacity could be promoted through a National Academies of Science panel. Given some states' actions to regulate chemicals of concern, such coordination should involve the relevant state agencies in order to gain knowledge of regulatory obstacles and the assessment of compliance and benefits. Greater international coordination and data sharing would allow for better chemical evaluation as well; for example, U.S. and European environmental regulators are unable to share chemical data that companies submit to European authorities under REACH.[70] The FDA could play a larger role in chemical safety in the future. The agency recently issued a final rule that over-the-counter antibacterial handwash products can no longer contain 19 active ingredients, including triclosan and tricloban, because manufacturers failed to demonstrate that the ingredients were safe and effective.[71]

Despite the potential positive changes related to chemical class evaluation and regulation, comprehensive chemical reform

DOI: 10.1021/acs.est.6b04980
Environ. Sci. Technol. 2016, 50, 12584−12591

remains warranted. Historically, federal regulatory action on chemicals has been limited in scope and focused on pollution management rather than pollution prevention. Social scientists find that such action can give the public a false sense of protection and lessen demand for more comprehensive reform.[72] In the case of PFASs, broader attention to the entire class of compounds is particularly important in light of increasing evidence of drinking water contamination and growing community organizing around health concerns.

AUTHOR INFORMATION

Corresponding Author

*Phone: (509) 527-5124; fax: (509) 527-5026; e-mail: cordneaa@whitman.edu.

ORCID

Alissa Cordner: 0000-0001-5223-2848

Author Contributions

All authors participated in data collection and analysis. All authors contributed to the writing and revising of the manuscript. All authors gave approval to the final version of the manuscript.

Funding

This research was supported by the National Science Foundation (SES-1456897).

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This research was supported by the National Science Foundation (SES-1456897). This article has not been reviewed by the National Science Foundation, and the views expressed are solely those of the authors. We are grateful to Thomas Neltner for helpful comments on drafts of this article. We thank Yvette Niwa for her research assistance and Stephanie Knutson for her help compiling references. Finally, we express our sincere thanks to all those we have interviewed as part of this research.

REFERENCES

(1) Food and Drug Administration. Indirect food additives: Paper and paperboard components. *Fed. Regist.* **2016**, *81*, 5−8 Codified at 21 CFR 176..

(2) Egeghy, P. P.; Judson, R.; Gangwal, S.; Mosher, S.; Smith, D.; Vail, J.; et al. The exposure data landscape for manufactured chemicals. *Sci. Total Environ.* **2012**, *414*, 159−166.

(3) Judson, R.; Richard, A.; Dix, D. J.; Houck, K.; Martin, M.; Kavlock, R.; et al. The toxicity data landscape for environmental chemicals. *Environ. Health Perspect.* **2009**, *117* (5), 685−695.

(4) *What is the TSCA Chemical Substance Inventory*; United States Environmental Protection Agency: Washington, DC, 2010.

(5) Geiser, K.*Chemicals without Harm: Policies for a Sustainable World*; The MIT Press: Cambridge, MA, 2015.

(6) Vogel, S. A.; Roberts, J. A. Why the toxic substances control act needs an overhaul, and how to strengthen oversight of chemicals in the interim. *Health Aff.* **2011**, *30* (5), 898−905.

(7) *Essential Principles for Reform of Chemicals Management Legislation*; United States Environmental Protection Agency: Washington, DC, 2009.

(8) U.S. Code Title 15, Chapter 53. Toxic Substances Control, 2016; http://uscode.house.gov/view.xhtml?path=/prelim@title15/chapter53&edition=prelim.

(9) *Analog identification method*; United States Environmental Protection Agency: Washington, DC, 2012; https://www.epa.gov/tsca-screening-tools/analog-identification-methodology-aim-tool.

(10) *Occurrence and Use of Highly Fluorinated Substances and Alternatives*; Swedish Chemicals Agency: Stockholm, Sweden, 2015.

(11) Buck, R. C.; Franklin, J.; Berger, U.; Conder, J.; Cousins, I. T.; de Voogt, P.; Jensen, A. A.; Kannan, K.; Mabury, s.A.; van Leeuwen, S. P. Perfluoroalkyl and polyfluoroalkyl substances in the environment: Terminology, classification, and origins. *Integr. Environ. Assess. Manage.* **2011**, *7* (4), 513−541.

(12) *Perfluorinated chemicals (PFCs)*; United States Department of Health and Human Services: Research Triangle Park, NC, 2012.

(13) *Fourth National Report on Human Exposure to Environmental Chemicals*; United States Centers for Disease Control and Prevention: Atlanta, GA, 2009.

(14) Calafat, A. M.; Wong, L. Y.; Kuklenyik, Z.; Reidy, J. A.; Needham, L. L. Polyfluoroalkyl Chemicals in the U.S. Population: Data from the National Health and Nutrition Examination Survey (NHANES) 2003−2004 and Comparisons to NHANES 1999−2000. *Environ. Health. Perspect.* **2007**, *115* (11), 1578−1583.

(15) Lau, C.Perfluorinated compounds: An overview. In *Toxicological Effects of Perfluoroalkyl and Polyfluoroalkyl Substances*; DeWitt, C. J., Ed.; Springer International Publishing: Cham, 2015; pp 1−21.

(16) Buck, R. C.; Franklin, J.; Berger, U.; Conder, J.; Cousins, I. T.; de Voogt, P.; Jensen, A. A.; Kannan, K.; Mabury, s.A.; van Leeuwen, S. P. Perfluoroalkyl and polyfluoroalkyl substances in the environment: Terminology, classification, and origins. *Integr. Environ. Assess. Manage.* **2011**, *7* (4), 513−541.

(17) *2010/2015 PFOA Stewardship Program*; Environmental Protection Agency: Washington, DC, 2015; https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/20102015-pfoa-stewardship-program.

(18) *Drinking water health advisories for PFOA and PFOS*; Environmental Protection Agency: Washington, DC, 2016; https://www.epa.gov/ground-water-and-drinking-water/drinking-water-health-advisories-pfoa-and-pfos.

(19) *SC-4/17: Listing of perfluorooctane sulfonic acid, its salts and perfluorooctane sulfonyl fluoride*; Stockholm Convention: Stockholm, Sweden, 2009; http://chm.pops.int/TheConvention/ThePOPs/TheNewPOPs/tabid/2511/Default.aspx.

(20) *Prohibition of Certain Toxic Substances Regulations, 2012(SOR/2012−285)*; Environment Canada, 2016; http://ec.gc.ca/lcpe-cepa/eng/regulations/DetailReg.cfm?intReg=207.

(21) Post, G. B.; Cohn, P. D.; Cooper, K. R. Perfluorooctanoic acid (PFOA), an emerging drinking water contaminant: a critical review of recent literature. *Environ. Res.* **2012**, *116*, 93−117.

(22) *C8 Probable Link Reports*; C8 Science Panel, 2012; http://www.c8sciencepanel.org/prob_link.html.

(23) *Critical Review of Studies Conducted with ≥ C8 Perfluorinated Compounds Concerning Selected Endpoints*; United States Food and Drug Administration Toxicology Group 1: Washington DC, 2010.

(24) C-8 medical monitoring program; http://www.c-8medicalmonitoringprogram.com/.

(25) Neltner, T. G.; Kulkarni, N. R.; Alger, H. M.; Maffini, M. V.; Bongard, E. D.; Fortin, N. D.; et al. Navigating the U.S. Food Additive Regulatory Program. *Compr. Rev. Food Sci. Food Saf.* **2011**, *10* (6), 342−368.

(26) *Food Additives Amendment of 1958 Committee Report*; United States Senate Committee on Labor and Public Welfare: Washington, DC, 1958.

(27) Electronic code of federal regulations; http://www.ecfr.gov/cgi-bin/ECFR?SID=439faaf8d98340e96015b83aed9b0a7d&mc=true&page=faq.

(28) *1958 Food Additives Amendment*. Pub. L. No. 85−929, § 4, 72 Stat. 1784 (1958) (codified at 21 U.S.C. § 348 (1970)).

(29) Food and Drug Administration. *Modernization Act of 1997*; United States Food and Drug Administration: Washington, DC, 1997.

(30) *Final Determination Regarding Partially Hydrogenated Oils*; Food and Drug Administration: Washington, DC, 2015; https://www.federalregister.gov/documents/2015/06/17/2015-14883/final-determination-regarding-partially-hydrogenated-oils.

DOI: 10.1021/acs.est.6b04980
Environ. Sci. Technol. 2016, 50, 12584−12591

(31) Food and Drug Administration. Food additive petitions: American Chemistry Council. *Fed. Regist* **2012**, *77*, 9608−9610.
(32) Food and Drug Administration. Indirect food additives: Adhesives and components of coatings; Notice of final rule. *Fed. Regist.* **2013**, *78*, 41840−41843.
(33) *Food Additive Regulations Amended to No Longer Provide for the Use of BPA-Based Materials in Baby Bottles, Sippy Cups, And Infant Formula Packaging*; United States Food and Drug Administration: Silver Spring, MD, 2016; http://www.fda.gov/Food/IngredientsPackagingLabeling/FoodAdditivesIngredients/ucm064437.htm#regulations.
(34) *Update on Perfluorinated Grease-Proofing Agents*; Food and Drug Administration: Silver Spring, MD, 2015; http://www.fda.gov/food/ingredientspackaginglabeling/packagingfcs/notifications/ucm308462.htm.
(35) National Resources Defense Council. Filing of Food Additive Petition. *Fed. Regist.* **2015**, *80*, 13508 Codified at 21 CFR 176; pp 2..
(36) National Resources Defense Council. Filing of Food Additive Petition. *Fed. Regist* **2015**, *80*, 13508 Codified at 21 CFR 176..
(37) *Memorandum of Meeting Between FDA CFSAN and the Society of the Plastics Industries*; United States Food and Drug Administration: Washington, DC, 2015.
(38) Comment from Society of the Plastics Industry Inc (Keller and Heckman LLP); FDA Docket # FDA-2015-F-0714, 2015; https://www.regulations.gov/document?D=FDA-2015-F-0714-0006.
(39) *Survey of Fluoropolymers Division Members from Various Industries re: Comment from Members of the Society of the Plastics Industry*; Inc (Keller and Heckman LLP); FDA Docket # FDA-2015-F-0714, 2015; https://www.regulations.gov/document?D=FDA-2015-F-0714-0009.
(40) Stewart, S.Munchie box scandal: Scotland's lastest fast-food fad is bursting with calories but it's the packaging that could kill you. *Scottish Daily Record***2016**, 1/11/16.
(41) *News Reports on Pizza Box Safety Misleading to Public*; American Forest & Paper Association: Washington, DC, 2016.
(42) FDA*bans three toxic chemicals from food wrapping - too little, too late*; Environmental Working Group, 2016; http://www.ewg.org/release/fda-bans-three-toxic-chemicals-food-wrapping-too-little-too-late.
(43) Cordner, A.*Toxic Safety: Flame Retardants, Chemical Controversies, and Environmental Health*; Columbia University Press: New York, 2016.
(44) Vogel, S. A.*Is it Safe?: BPA and the Struggle to Define the Safety of Chemicals*; University of California Press: Berkeley, CA, 2012.
(45) FDA sued for delay in deciding perchlorate food additive petition; http://blogs.edf.org/health/2016/03/31/perclorate-lawsuit/?utm_source=feedburner&utm_medium=email&utm_campaign=Feed%3A+nanotechnologynotes+%28Chemicals+%26+Nanomaterials%29.
(46) Food and Drug Administration. Federal Register. Filing of Food Additive Petition: 21 CFR Parts 175−178. *Fed. Regist.***2016**, *81* (98), 31877−31879.
(47) *Protecting Public Health and the Environment: Implementing the Precautionary Principle*; Raffensperger, C., Tickner, J., Eds.; Island Press: Washington, DC, 1999.
(48) Kriebel, D.; Tickner, J. Reenergizing public health through precaution. *Am. J. Public Health* **2001**, *91* (9), 1351−1355.
(49) Kriebel, D. The reactionary principle: Inaction for public health. *Occup. Environ. Med.* **2007**, *64* (9), 573−574.
(50) Aviation Gasoline. https://www.faa.gov/about/initiatives/avgas/.
(51) Lead. https://www.epa.gov/lead.
(52) Etzion, D.; Davis, G. F. Revolving Doors? A Network Analysis of Corporate Officers and U.S. Government Officials. *Journal of Management Inquiry.* **2008**, *17* (3), 157−161.
(53) Walker, E. T.; Rea, C. M. The Political Mobilization of Firms and Industries. *Annu. Rev. Sociol* **2014**, *40*, 281−304.
(54) Markowitz, G. E.; Rosner, D.*Deceit and Denial: The Deadly Politics of Industrial Pollution*; University of California Press: Berkeley, CA, 2002.
(55) Michaels, D.*Doubt Is Their Product: How Industry's Assault on Science Threatens Your Health*; Oxford University Press: New York, 2008.
(56) Oreskes, N.; Conway, E.*Merchants of Doubt: How a Handful of Scientists Obscured the Truth on Issues from Tobacco Smoke to Global Warming*; Bloomsbury Press: New York, 2010.
(57) *Potential designated chemicals: perfluoroalkyl and polyfluoroalkyl substances (PFASs)*; Biomonitoring California, 2015; http://www.biomonitoring.ca.gov/sites/default/files/downloads/PotenDesigPFASs_031315.pdf.
(58) Gamson, W. A.; Croteau, D.; Hoynes, W.; Sasson, T. Media Images and the Social Construction of Reality. *Annu. Rev. Sociol* **1992**, *18*, 373−93.
(59) Boykoff, M. T. We speak for the trees: Media reporting on the environment. *Annu. Rev. Environ. Resour.* **2009**, *34*, 431−57.
(60) Brown, P.; Zavestoski, S. M.; McCormick, S.; Mandelbaum, J.; Luebke, T. Print media coverage of environmental causation of breast cancer. *Sociol. Health Illn* **2001**, *23* (6), 747−775.
(61) Rich, N. The lawyer who became DuPont's worst nightmare.*New York Times Magazine*; January 6, **2016**; pp 36.
(62) Blum, A. Tackling toxics. *Science* **2016**, *351* (6278), 1117−1117.
(63) Cordner, A.; Brown, P. A Multisector Alliance Approach to Environmental Social Movements: Flame Retardants and Chemical Reform in the United States. *Environmental Sociology* **2015**, *1* (1), 69−79.
(64) Lemos, M. C.; Agrawal, A. Environmental Governance. *Annu. Rev. Environ. Resources* **2006**, *31*, 297−325.
(65) *Players and Arenas: The Interactive Dynamics of Protest*; Duyvendak, J., Duyvendak, J., Duyvendak, J. W., Eds.; Amsterdam University Press: Amsterdam, 2015.
(66) Armstrong, E. A.; Bernstein, M. Culture, Power, and Institutions: A Multi-Institutional Politics Approach to Social Movements. *Sociological Theory.* **2008**, *26* (1), 74−99.
(67) Blum, A.; Balan, S. A.; Scheringer, M.; Trier, X.; Goldenman, G.; Cousins, I. T.; et al. The Madrid statement on poly-and perfluoroalkyl substances (PFASs). *Environ. Health Perspect.* **2015**, *123* (5), A107−A111.
(68) Gulbrandsen, L. H. Dynamic governance interactions: Evolutionary effects of state responses to non-state certification programs. *Regulation & Governance* **2014**, *8*, 74−92.
(69) Eberlein, B.; Abbott, K. W.; Black, J.; Meidinger, E.; Wood, S. Transnational business governance interactions: Conceptualization and framework for analysis. *Regulation & Governance* **2014**, *8*, 1−21.
(70) Hegstad, M. EPA Presses Industry to Provide Flame Retardants' Data for TSCA Review. *Inside EPA* **2013**.
(71) FDA issues final rule on safety and effectiveness of antibacterial soaps; http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm517478.htm?source=govdelivery&utm_medium=email&utm_source=govdelivery.
(72) Szasz, A.*Shopping Our Way to Safety: How We Changed from Protecting the Environment to Protecting Ourselves*; University of Minnesota Press: Minneapolis, MN, 2007.

DOI: 10.1021/acs.est.6b04980
Environ. Sci. Technol. 2016, 50, 12584−12591