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Abstract

Earlier research using the directed technical change framework argues that with the right mix of policies, governments can steer firms' R&D efforts away from harmful technologies toward supposedly cleaner alternatives. This article puts that assumption to the test by examining the impact of the 2004 Stockholm Convention, which banned 12 highly toxic persistent organic pollutants (POPs), on the development of alternative chemical compounds. Does regulation truly drive innovation toward safer substitutes, or does it create new risks under a different guise? Our results show that rather than steering innovation towards safer alternatives, the Stockholm Convention has incentivized the development of patents containing s.c. "regrettable" chemicals – i.e. chemicals that, while not banned under the Convention, exhibit POP-like characteristics, particularly high toxicity and persistence. Our study suggests that a closer inspection of the substitute technologies is crucial to understanding the effectiveness of incentives set to replace dirty technologies with cleaner ones.

Keywords: directed technical change; persistent organic pollutants (POPs), Stockholm Convention, policy evaluation, patent toxicity.

JEL classification: Q55, Q58, O31, O33

1 Introduction

Technological change is a key driver of economic and societal progress. A central question is why, in the search for technological solutions, some technologies prevail over others, exploring the forces behind technology selection (Nelson and Winter, 1982; Dosi, 1982; Arthur, 2009). While early policy concerns focused on addressing underinvestment in innovation through interventions that allowed firms to appropriate R&D returns (Arrow, 1962), the emphasis today has shifted away from merely ensuring adequate investment in R&D, to ensuring that these investments are channeled into the "right" directions—particularly to avoid technological advancements that could have adverse effects on society or the natural environment (Castaldi et al., 2024).

A prominent framework for understanding the direction of technical change—particularly the shift from polluting to cleaner technologies—is the theory of "directed technical change" (Acemoglu, 2002, 2023; Hicks, 1932). According to this view, economic agents respond to market signals such as prices and potential market size by steering innovation in particular directions. When these signals are aligned with social objectives, the outcome is desirable. But when they are not, there is room—and indeed, a need—for policy intervention. By adjusting incentives appropriately, policymakers can redirect innovation toward cleaner alternatives. Empirical studies support this logic, showing that when the right incentives are in place, firms shift their R&D investment from dirty to supposedly cleaner technologies (Aghion et al., 2016; Dugoua, 2023; Dugoua and Gerarden, 2023).

In this article, we seek to reassess this framework and challenge the underlying policy implications, specifically focusing on the case of s.c. "regrettable" substitutes in chemistry, understood as replacements for known hazardous chemicals that turn out to have similar or even new harmful effects (Zimmerman and Anastas, 2015). We argue that a weak point in the directed technical change literature lies in its definition of what constitutes a "cleaner" technological alternative. Typically, alternatives are deemed cleaner because they address specific harms identified in previous technologies—such as reducing CO2 emissions, water usage, or reliance on conventional plastics. However, the existing literature often overlooks the fact that, while these alternatives may mitigate one source of harm, they may simultaneously introduce new risks to the environment or society. This is not to deny the value of R&D investments in alternative technologies but to highlight that, by failing to account for these additional dimensions, the current framework offers an incomplete view of technological change and its directions.

As research increasingly demonstrates the effectiveness of corrective incentives for firms, it becomes ever more important to assess whether these incentives not only steer R&D towards technological alternatives but, crucially, whether these alternatives are truly safer than the original technologies across multiple dimensions. If the answer is affirmative, it would strengthen the case for the directed technical change approach and its associated policy recommendations. On the other hand, if alternatives fail to meet this standard, it would underscore the need for a rethinking of the approach and the development of more effective policy solutions.

To explore this issue, we analyze chemical patents, focusing on substitutes for persistent organic pollutants (POPs)—a highly toxic and long-lasting class of chemicals. In 2004, the Stockholm Convention (SC or the Convention hereinafter) imposed a global ban or strict restrictions on 12 POPs, making it an ideal case to study the impact of regulatory action on technological alternatives. By combining patent analyses with computational toxicology (Biggi et al., 2022), we conduct toxicity assessments on over 90,000 substitute patents filed in patent offices worldwide between 1965 and 2014, covering some 1.8 million unique chemical compounds. This analysis allowed us to neatly identify the universe of "regrettable patents", defined here as patents that do not contain any of the 12 POPs subject to the Stockholm Convention ban in the chemical formulation, but include chemicals that possess similar persistent toxicities (hence "regrettable").

We apply a Difference-in-Difference (DID) estimation strategy to compare regrettable patents against a suitable control group. We find that the SC resulted in an average increase of 2.74 regrettable patents globally, and 4.95 in the U.S., compared to the control group. When adjusted for the pre-2004 yearly averages of regrettable patents (1.83 globally and 3.67 in the U.S.), these figures imply a 150% rise in regrettable patents worldwide and a 135% rise in the U.S. This suggests that rather than steering innovation towards safer alternatives, the Convention may have incentivized the creation of more patents covering regrettable chemical substitutes.

Our findings lay the groundwork for rethinking the dominant approach to directed technical change. They highlight the need for further research into the phenomenon of regrettable substitutes across different technological domains and offer a starting point for a deeper exploration of how firms shape their R&D agendas and the direction of their technological trajectories. Understanding what drives companies to choose regrettable substitutes over safer alternatives is critical for designing more effective policies. We see this study as a first step in a broader research agenda that can provide an informed contribution to the literature on the directions

of technological change.

The article is structured as follows. Section 2 provides an overview of the relevant literature, identifies the research gap, and presents our central research question. Section 3 introduces the empirical case, outlining the context of our study. Section 4 details the data and methodology. Section 5 presents the empirical results, and Section 6 concludes with a discussion of key findings and implications.

2 Background literature and gaps

The 'directed technical change' framework (Acemoglu, 2002; Hicks, 1932) rests on the assumption that economic actors respond rationally to market signals and incentives—prices, wages, market size, subsidies, etc.—when determining the allocation of their innovation efforts. Scholars in this tradition recognize that market failures arise from a misalignment between private incentives and social goals (often caused by externalities that are not fully internalized). This divergence leads to the proliferation of 'inappropriate' technologies that are detrimental from a societal perspective (Acemoglu, 2002). Research in this tradition often seeks to explain how firms adjust to regulatory interventions designed to correct these failures ex post, i.e., once innovations are already in the market (Dugoua, 2023; Aghion et al., 2016), and under what conditions market incentives stimulate inventors to shift from dirty to clean technologies (Dugoua and Gerarden, 2023) or to more beneficial outcomes, as, e.g., better pharmaceutical treatment strategies (Budish et al., 2015). Policy-wise, the directed technical change literature contends that setting proper incentives can effectively steer corporate R&D toward socially beneficial goals.

Importantly, in the ongoing debate around the determinants of the direction of technical change, research tends to resort to a binary classification of technological alternatives categorising them as either "clean" (green or addressing desirable social needs) or "dirty" technologies (polluting or hazardous for health) often based on conventional, high-level product groupings (e.g. Aghion et al., 2016; Dechezleprêtre et al., 2014; Dugoua and Gerarden, 2023). Classic distinctions between "clean" vs. "dirty" technologies include combustion engines vs. electric vehicles in the automotive sector (Aghion et al., 2016), fossil fuels vs. renewable sources in energy (Veugelers, 2012; Romagnoli, 2024) or climate-resistant genetically modified organisms vs. traditional crops in agriculture (Moscona and Sastry, 2023).

A key problem with these categorizations is that they implicitly assume that technologies eliminating the contested source of harm—such as CO2 emissions or pollutants flagged as dangerous by the relevant authorities —are unambiguously superior, cleaner alternatives. By focusing on a single contested dimension of the technology's impact, they tend to ignore potential other side effects or sustainability challenges that may emerge from the allegedly cleaner alternative. For instance, electric cars are cleaner in terms of the fine particulate emissions generated by users and net zero targets, but they are also found to generate considerable negative environmental and socio-economic externalities in the value chain (Haghani et al., 2024).

Perhaps no technological domain illustrates the unintended consequences of alternative technologies more clearly than chemical formulations. While new chemical solutions are often introduced to mitigate the harms of existing compounds—for instance by reducing certain types of toxicity or eliminating key pollutants—they may generate new problems. For this reason, the specialized chemistry literature has coined the term "regrettable substitutions" (Zimmerman and Anastas, 2015), wherein alternatives perceived as more desirable under one dimension can inadvertently introduce new hazards. The typical case is the substitution of bisphenol A (BPA), an organic compound used predominantly in food and beverage cans, to bisphenol S, an allegedly less toxic substitute that turned out to be as oestrogenic and toxic to embryos as BPA (Trasande, 2017).

We suggest that the prevalent approach in the directed technological change literature has so far overlooked the problem of "regrettable" technological alternatives. This oversight constitutes an important gap in the literature for two reasons. First, at a conceptual level, the failure to recognize the risks embedded in technological alternatives distorts how we understand corporate R&D strategies and their role in shaping technological trajectories. By assuming that these alternatives, responding to stricter regulation, are superior, we overlook the strategic choices firms make in directing innovation; in other words, if we fail to distinguish a truly cleaner technology from a regrettable substitute, we cannot determine whether a company is responding to incentives and policies by developing genuinely cleaner strategies—a more transformative approach steering innovation towards more sustainable technologies —or merely addressing a specific problem without a broader transformative agenda, thereby creating new risks for the market.

Relatedly, the second reason is that this ambiguity poses significant policy concerns, as extant policies or incentives may foster steady cycles of regrettable substitutions, potentially

undermining long-term sustainability goals. We think that these elements of concern are important to the directed technical change literature, which may be overly optimistic about the power of incentives and regulatory action to fix past problems and steer innovation in the "right" direction.

3 The empirical case

Synthetic chemical compounds are integral to modern life. Along with the emergence of modern chemistry, molecular structures not found in nature became ubiquitous in the products we consume; they permeate everything from food and beverages, personal care items, and household goods, to pesticides. Often, they exhibit numerous beneficial properties and have led to increasing standards of living and a rise in social welfare in general. Nevertheless, synthetic molecules can also be dangerous and harm health and the environment. According to Eurostat (2024), more than 300 million tons of chemicals were consumed in the EU in 2018 and more than two-thirds of this amount were chemicals that are classified as hazardous to health. Among the several examples, polybrominated diphenyl ether flame retardants and organophosphate insecticides still appear to be produced in large quantities despite their adverse impacts on human health and the environment (Kaushal et al., 2020; de Boer et al., 2022). Similar examples can be found in almost any industry. Food additives and preservatives are often considered safe in small quantities, but their accumulation and interactions induce food cravings, leading to chronic health conditions such as obesity and diabetes (Lane et al., 2024). Cosmetics and household products expose consumers to hazardous chemicals like parabens and phthalates, which are associated with hormone disruption and cancer (Zuccarello et al., 2018). Importantly, besides the health and environmental impacts, hazardous chemicals also represent a burden for public finances: for instance, the cost of human health damages caused by endocrine-disrupting chemicals such as phthalates widely used as plasticizers and in fragrance packages, flame retardants, and pesticides has been estimated in the U.S. at 2.33% of GDP and 1.23% of GDP in the EU (Attina et al., 2016).

While examples abound, our interest here is in a specific class of highly dangerous chemicals known as persistent organic pollutants (POPs). POPs are a class of compounds with beneficial properties in pest and disease control, and with industrial applications from lubrication to repellent surfaces. The first group of 12 POPs, sometimes referred to as the "dirty dozen", was

widely used during the boom in industrial production and intensive agriculture after World War II. POPs accumulate in ecosystems and living organisms and are linked to serious long-term health issues, including cancer (Buñay et al., 2023).

The impacts of POPs were originally signaled by environmental scientist Rachel Carson through her book Silent Spring (1962), which highlighted how POPs like DDT, chlordane, dieldrin, aldrin, and endrin among others, through their bioaccumulative toxic properties, posed risks to human health and the environment. Her book catalyzed environmental movements, governments, and scientific communities began recognizing the need to regulate such chemicals. By the early 1970s, public concern over pesticide use grew, and in 1972, DDT was banned in the U.S., marking a major victory for environmental protection. This period saw the creation of organizations such as the Environmental Protection Agency (EPA) in the U.S., which began taking steps to regulate toxic chemicals and address pollution. Alongside these national efforts, international discussions around the regulation of hazardous substances also gained momentum since it was clear that the issue of persistent pollutants was not confined to one country or region but was a global challenge requiring coordinated international action.

However, it was not until 2001 that a formal treaty - known as the Stockholm Convention (SC or the Convention) - was signed, to be ratified in 2004. The treaty aimed to eliminate or restrict the "dirty dozen" POPs and provided mechanisms for international cooperation and support for developing nations. It entered into force on May 17, 2004, and expanded to include additional harmful chemicals over time. We consider the ratification of the Convention as our treatment because, in the context of these kinds of pollutants, this is without doubt a milestone treaty, legally binding for 110 parties worldwide.

In this paper, we examine the impact of the 2004 entry into force of the SC on the development of technological alternatives. Our central question is whether the SC successfully steered R&D toward safer substitutes, or whether it simply encouraged the proliferation of regrettable alternatives.

4 Methodology

The 2004 ratification of the SC represents our treatment, and we evaluate how it affects the development of substitutes for the 12 POPs. Our empirical analysis is based on patent application data spanning from 1965 to 2014.

We begin from 1965 to capture the early development of chemical alternatives, ensuring a long enough pre-SC period to observe trends in innovation before regulatory intervention. The endpoint of 2014 reflects the last year for which our patent databases provide full and reliable coverage.[1] This timeframe allows us to conduct a meaningful post-treatment analysis.

To accomplish this goal we combine multiple data sources: we first identify patents related to the 12 POPs (POP patents) using their unique CAS Numbers from the SciFinder-n database, supplementing them with standard patent data from PATSTAT (version Autumn, 2023). To find alternative chemicals —compounds functionally and structurally similar to the banned POPs but not covered by the 2004 SC—we use the Chemical Entities of Biological Interest (ChEBI) Ontology. The ChEBI Ontology is a structured classification of molecular entities. It is developed and maintained by the European Bioinformatics Institute (EBI) and provides a comprehensive database of chemical substances, including their structures, properties, and relationships. Patents containing these alternatives (substitute patents) are then retrieved via SciFinder-n and enriched with PATSTAT data. Finally, we assess the toxicity of chemicals covered by the substitute patents using the VEGA Hub software, allowing us to distinguish between patents containing regrettable substitutes (regrettable patents) and safer patents. In our empirical strategy we employ standard DID approach, using as a control group a selected group of safer patents that are not likely subject to the SC.

4.1 Patent Data

Following prior literature we use patent documents as a measure of innovation in the chemical industry (Jayaraj and Gittelman, 2018; Dugoua, 2023). Chemical patents have two advantages. First, molecules can be precisely tracked in patent records, allowing researchers to identify their development and the actors involved. Second, the advanced computational techniques in chemistry allow for the prediction of these compounds' multifaceted characteristics, surpassing simplistic categorizations of "dirty" or "clean" based on the presence or absence of a specific chemical compound. These methods can predict various properties, including different types of human health toxicities and environmental impacts, thus providing a nuanced understanding of the direction of technical change and the associated societal impacts. In other words, chemical patents provide explicit molecular details, including each compound's structural composition

[1] Our observation period ends in 2014, as the combination of our data sources, including patent documents and related chemical compounds, provides consistent and comparable coverage up to that year.

and role in the invention.

To systematically link chemical compounds with patent documents, we rely on CAS SciFinder-n, a database developed by the Chemical Abstracts Society (CAS), which offers extensive coverage of chemical patents from patent offices across different countries worldwide, including the United States Patent and Trademark Office (USPTO), the European Patent Office (EPO), and the Japan Patent Office (JPO). CAS SciFinder-n enables precise mapping of chemical compounds to their associated patent documents, allowing for a structured analysis of inventive dynamics. A key feature of this database is that it classifies compounds based on their functional roles played in the patent—such as whether a given chemical compound represents e.g. a catalyst, an excipient, or plays another active role in the chemical reaction —providing full information into their contribution to the patented invention. Additionally, it assigns a unique CAS Registry Number (hereinafter CAS Number) to each chemical compound to ensure the accurate and consistent identification of chemical compounds across international databases.

4.1.1 POP patents

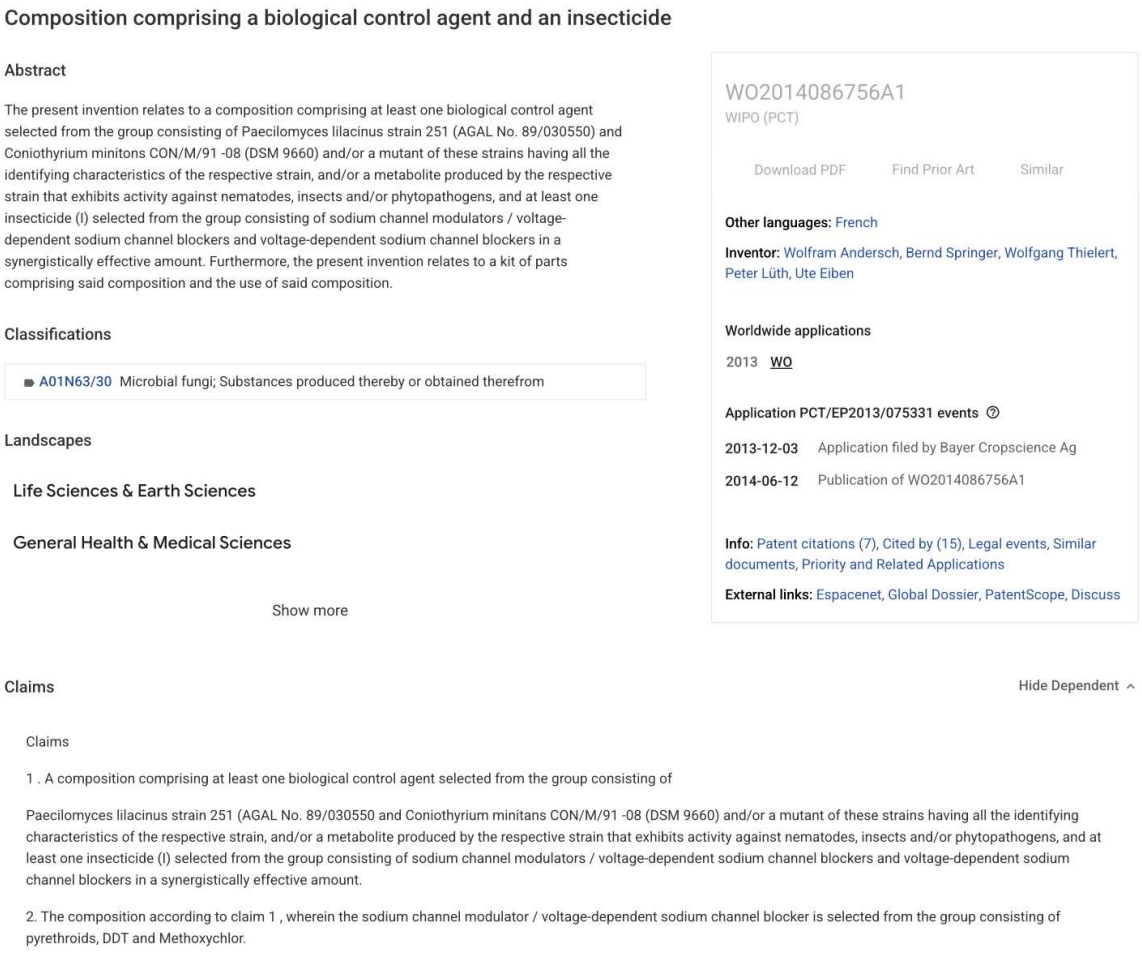
Using the SciFinder database, we first retrieve patents that include in their formulations at least one of the original 12 POPs subject to the 2004 SC ban (hereinafter POP patents, see Table 1 for an overview). We consider only patents where at least one of the 12 POPs is included among the ingredients (e.g. DDT used as an ingredient in the patented chemical compound) (see Figure 1 for an example), which in Scifinder is characterized by the following roles: "use", "use as a part of a mixture" or "use in preparation", etc.[2] To clarify, selecting specific roles ensures that patents are excluded from the analysis if a POP is mentioned only as example or if a POP is included because the patent focuses on developing a chemical compound designed to eliminate POP contamination (in such cases, SciFinder labels the chemical as a "substance removed" or a "removing or purifying agent"). We match the retrieved patents with PATSTAT information. By merging these sources, we find 354 patent applications and 93 DOCDB patent families filed worldwide over the period 1965-2014, corresponding to 11 out of the 12 POPs banned under the Convention.

[2]It is to note that roles connected to the use of a compound in a patent are not limited to those listed here, but include additional categories such as Bioindustrial Manufacture, Byproduct, Industrial Manufacture, Synthetic Preparation, Reactant, Uses, Agricultural Use, Analytical Reagent Use, Catalyst Use, Food or Feed Use, Modifier or Additive Use, Polymer in Formulation, Miscellaneous. See CAS-Scifinder (2024) for additional references.

Table 1: POPs main uses, CAS number, applications, type of exposure and effects

Chemical	CAS Number	Category	Main Uses and Applications	Main Types of Exposure and Effects
Aldrin	309-00-2	Pesticide	Applied to soils to kill termites, grasshoppers, corn rootworm, and other insect pests	Humans are mostly exposed to aldrin through dairy products and animal meats
Chlordane	57-74-9	Pesticide	Used to control termites and as an insecticide on agricultural crops	Human immune system and human carcinogen
Dichlorodiphenyltrichloroethane (DDT)	50-29-3	Pesticide	Pesticide used to control insects that spread diseases, such as malaria, and also on crops, especially cotton	Liver effects and carcinogenesis. Effects on children's health and development. Exposure linked to preterm delivery, reduced birth weight, and shortened lactation
Dieldrin	60-57-1	Pesticide	Used to control termites and textile pests	Long-term exposures have been associated with chronic health effects
Endrin	72-20-8	Pesticide	Insecticide used on crops such as cotton and grains, also used to control rodents	Endrin poisoning in humans primarily affects the nervous system. Food contaminated with endrin has caused several clusters of poisonings worldwide, especially affecting children
Heptachlor	76-44-8	Pesticide	Used to control soil insects and termites	Possible human carcinogen. Food is the major source of exposure for humans
Hexachlorobenzene	118-74-1	Industrial chemical	Used to kill fungi that affect food crops	Crosses the placenta to accumulate in fetal tissues and is transferred in breast milk. Extremely toxic to aquatic creatures. Risk of bioaccumulation in an aquatic species is high.
Mirex	2385-85-5	Industrial chemical	Insecticide mainly used to control fire ants	Effects on organisms combined with its persistence suggest that mirex presents a long-term hazard for the environment
Toxaphene	8001-35-2	Pesticide	Insecticide used on cotton, cereal grains, fruits, nuts, and vegetables. Also used to control ticks and mites in livestock	Exposure can cause damage to lungs, nervous system, kidneys and can be fatal
Polychlorinated Biphenyls (PCB)	1336-36-3	Industrial chemical	Range of compounds used in industry as heat exchange fluids, in electric transformers and capacitors, and as additives in paint, carbonless copy paper, and plastics	PCB are associated with cancer in humans, such as cancer of the liver and biliary tract
PCDD/PCDF	39227-53-7; 39227-54-8; 54536-18-4; 50585-39-2; 54536-19-5; 38178-38-0; 82291-26-7; 82291-27-8; 82291-28-9; 29446-15-9;33857-26-0; 38964-22-6; 54536-17-3; 39227-58-2;69760-96-9; 82291-30-3; 82291-31-4; 82291-32-5 82291-33-6; 67028-17-5 82306-61-4; 82306-62-5; 82306-63-6; 82306-64-7 82306-65-8; 33857-28-2; 30746-58-8; 71669-25-5; 67028-18-6; 53555-02-5 71669-26-6; 71669-27-7; 71669-28-8; 71669-29-9; 71665-99-1; 40581-90-6 67323-56-2; 40581-91-7; 34816-53-0; 71669-23-3;62470-54-6; 33423-92-6 71669-24-4; 50585-46-1; 62470-53-5; 40581-93-9;40581-94-0; 1746-01-6 67028-19-7; 39227-61-7; 71925-15-0; 71925-16-1; 82291-34-7; 40321-76-4 71925-17-2; 71925-18-3; 82291-35-8; 71998-76-0; 82291-36-9; 58802-08-7 82291-37-0; 82291-38-1; 58200-66-1; 58200-67-2;58200-68-3; 39227-28-6 57653-85-7; 64461-98-9; 58200-69-4; 19408-74-3; 39227-62-8; 58802-09-8 35822-46-9; 58200-70-7; 3268-87-9	Byproducts of production of other chemicals	Produced unintentionally during the manufacture of pesticides, emitted through the burning of waste and in all incomplete combustion	Acute lethality; Body weight loss; Carcinogenesis; Dermal toxicity; Fatty liver; Genotoxicity

Figure 1: Example of a DDT patent



Source: own elaboration from Google Patents.

4.1.2 Ontology-based substitute patents

A key challenge in this study is identifying technological alternatives to the 12 POPs. Alternatives (or substitutes) are chemical compounds that perform the same or similar chemical functions as the POPs but are not directly subject to the SC ban. Guided by cheminformatics experts and established classification methods, we use the ChEBI Ontology, which categorizes chemical compounds based on molecular structure and function, to systematically map POPs to their closest substitutes. For example, DDD (Dichlorodiphenyldichloroethane) is a well-known alternative to DDT—an organochlorine insecticide structurally similar to DDT but initially considered less toxic (Holder, 1986). After the ban of DDT, DDD has been widely used in agriculture and for public health purposes (Van den Berg, 2009).

Through this approach, we could identify 283 chemical substitutes for POPs (listed in Appendix Figure A2). Using CAS SciFinder-n and PATSTAT we constructed a novel database containing the universe of patents that include, among their active ingredients, chemicals with ontology-based similarities to the original POPs (ontology-based substitutes). Over the study period, our database includes 92,760 POP substitute patent applications and 21,305 DOCDB patent families (hereinafter patent families) worldwide, covering 1,826,483 unique chemical compounds. We now outline the approach adopted to differentiate regrettable patents from those representing safer alternatives.

Regrettable patents In this section, we explain how we classify ontology-based substitute patents that contain regrettable chemical compounds (hereinafter referred to as "regrettable patents"). The SC defines POP as organic chemical substances with specific physical and chemical properties such that, once released into the environment, exhibit the following characteristics: (i) persistence: they resist biodegradation, remaining intact for exceptionally long periods and accumulating in the environment as well as in living organisms, including humans and (ii) high toxicity: they pose significant health risks to both humans and wildlife. Their toxic effects can include cancer, allergies, hypersensitivity, nervous system damage (both central and peripheral), reproductive disorders, and immune system disruption.

We rely on this classification to identify regrettable substitutes and their associated patents. To this end, we combine patent analyses with computational (or in silico) toxicology following the methodology proposed by Biggi et al. (2022). In silico toxicology uses mathematical models to predict any potentially undesirable or adverse effects of a chemical compound based on the

compound's chemical structure (Cherkasov et al., 2014; Zimmerman et al., 2020). This approach relies on statistical and machine-learning tools used to extract information from collections of property data associated with chemical substances (Benfenati et al., 2013; Van Noorden, 2018).

To systematically classify patents as containing regrettable substitutes, we analyze all chemical compounds that SciFinder classifies as being in "use" and similar notations in the patent document. This analysis is conducted using VEGA Hub (www.vegahub.eu), an open-source software developed by Istituto di Ricerche Farmacologiche Mario Negri IRCCS in Milan. VEGA Hub provides access to a vast array of predictive models for chemical toxicity assessment, covering various endpoints such as carcinogenicity, mutagenicity, bioaccumulation, and environmental persistence.[3] To classify patents as "regrettable" we searched for patents that contain at least a "regrettable" chemical compound, that is, a chemical formulation that has POP-like features, namely it is persistent and highly toxic for human beings and/or the environment.

To measure persistence, we predict toxicity by focusing on Persistent and Bioaccumulative (PB) endpoints. PB toxicity is evaluated using eight Quantitative Structure-Activity Relationship (QSAR) models, including IRFMN (covering soil, sediments, and water), KNN, Meylan, and the Mond-Gobas model (see Appendix Figure A3). Next, our assessment of the high toxicity of the chemicals is very conservative as we frame it by key toxicity endpoints from the EU REACH regulation, which identifies substances of very high concern, and is aligned with the United Nations Global Harmonized System of Classification and Labelling of Chemicals (GHS), which includes Carcinogenic, Mutagenic, and Reproductive (CMR) toxicity. In consultation with experts, we also consider three alternative environmental toxicity (ET) endpoints, reflecting chemicals harmful at three trophic levels—algae, invertebrates, and fish—given the critical role of aquatic toxicity in environmental hazard and risk evaluations. Based on standard practice in computational toxicology, CMR toxicity is assessed using nineteen QSAR models, such as CAESAR, ISS, IRFMN/ANTARES, and the P&G reproductive toxicity model (see Appendix Table A3). ET toxicity is determined through seven QSAR models targeting fish, daphnia magna, and algae, with classifications based on toxicity concentration thresholds (see Appendix Table A3).

These models predict whether a substance can be classified as PB, CMR or ET using a

[3]Other similar software tools for toxicity predictions using QSAR models include the Environmental Protection Agency (EPA) CompTox Chemicals Dashboard and the OECD QSAR Toolbox. In this study, we have chosen to use VEGA Hub software, as it enables large-scale analysis of chemical compounds, unlike EPA CompTox and the OECD QSAR Toolbox.

Consensus approach (Zakharov et al., 2019; Pore et al., 2025). This strategy integrates multiple model outcomes to refine predictions and reduce errors. By harmonizing the results across different systems, the Consensus approach overcomes the biases of individual models. The specialized literature in fact suggests that combining models enhances accuracy and broadens chemical space coverage, outperforming single-model predictions (Fuadah et al., 2024; Pore et al., 2025).

Additionally, it is important to highlight that each QSAR model provides a reliability score (i.e., high, medium, or low) reflecting the confidence in its predictions. These scores help assess how dependable the prediction is based on the model's applicability domain and consistency with similar compounds. In our analysis, we focus exclusively on predictions marked with high reliability, ensuring that only the most robust and credible results are considered.

Following these QSAR predictions, a chemical is classified as "regrettable" if it contains compounds that meet any of the following criteria: PB *and* CMR, PB *and* ET, or PB, CMR, *and* ET. This classification approach enables the precise identification of chemical substitutes that exhibit similar persistence and toxicity to POPs but are not covered by the 2004 SC ban.

Using this methodology, we identified 20,132 patents and 3,943 patent families containing regrettable chemicals.

Safer patents Finally, in the universe of ontology-based substitutes, we classify "safer" patents as those that do not contain chemical compounds classified as PB, CMR, or ET in their formulations—meaning they do not possess any POP-like features. However, we acknowledge that these chemicals may not be entirely safe, as this group could include other less concerning forms of toxicity (e.g., endocrine disruptors or liver toxicity). Our classification only includes the most hazardous levels of toxicity, and it is therefore very conservative.

Using this approach, we identified 47,701 safer patents and 11,624 patent families.

Purgatory patents Among ontology-based substitute patents, we identify a third category, which we refer to as "purgatory patents," as they fall between the regrettable and safer groups. These patents involve chemicals that may be persistent (PB), CMR, or ET; however, unlike truly regrettable patents, they do not combine high toxicity (CMR or ET) with persistence (PB). This group comprises 24,967 patents and 5,738 patent families. We exclude this group from our main empirical analyses.

4.2 Data overview

Table 2 provides an overview of the patents and patent families by the typologies presented in the earlier section - i.e. POP, ontology-based substitute and the subcategories: regrettable, safer, and purgatory (panel A).[4] In panel B we show the number of ontology-based substitute patents (patent families and patents) for each POP.

Table 2: Dataset composition

Panel A	worldwide	
Type	patent families	patents
a) POP patents	93	354
b) ontology-based substitute patents:	21,305	92,760
b1) regrettable patents	3,943	20,132
b2) safer patents	11,624	47,701
Panel B	**worldwide**	
Ontology-based substitutes for:	patent families	patents
Aldrin	342	3,587
Chlordane	19,825	92,544
DDT	150	1,009
Dieldrin	316	3,391
PCDD/PCDF	12,297	51,797
Endrin	316	3,391
Heptachlor	19,821	92,539
Hexachlorbenzene	2,539	14,516
Mirex	294	3,154
PCB	95	467
Toxaphene	4	50

Note: The table reports the composition of the dataset used in the analysis at the patent application-level and DOCDB family-level. The data cover the patenting activity of 11 POPs and their ontology-based chemical substitutes in 89 patent offices worldwide over the period 1965-2014. Note that a patent can be assigned as a substitute to more than one POP.

Over our period of observation (1965-2014), the set of identified patents (POP and their ontology-based substitutes) are filed in 89 patent offices worldwide. The patent office that registers the highest number of filed patents (POPs and substitutes) is the U.S., followed by EPO, and by the patent offices of Japan, China, Germany, Canada, South Korea, Australia and Taiwan (see Appendix Figure A4). These 10 jurisdictions represent more than 70% of the patent applications filed worldwide in these technologies. In terms of DOCDB family size, the average (median) patent in our sample is filed in 7 (6) jurisdictions worldwide (the full distribution is shown in Appendix Figure A8).

Figure 2 (panel A) shows the number of patent families filed worldwide and over time, including the 12 POPs (left axis), the universe of ontology-based substitute patent families,

[4]Note that POP patents do not include Mirex patents, because no such patents exist in the relevant databases, while substitute patents exist for Mirex.

and the subgroups of regrettable and safer patent families (right axis). Figure 2 (panel B) shows the same trends for the U.S. In both cases, we observe an increase in all types of patents, including the 12 POP patents - although the numbers of these latter patents are very limited. Possibly these patents respond to the residual demands for POP chemicals in countries that poorly regulate these substances (Biggi et al., 2024). For example, some POPs continue to be used in certain regions, particularly in parts of Asia, where regulatory enforcement is less stringent (Van den Berg, 2009). Both regrettable and safer patents appear to grow over time.

Figure 3 plots the average share of harmful compounds in regrettable patents filed worldwide over time. Panel A shows that the share of PB, CMR and ET compounds has decreased starting in the 1980s. Instead, the trends displayed in panel B and panel C show that the share of PB and CMR compounds and the share of PB and ET compounds have increased starting around the ratification of the SC.

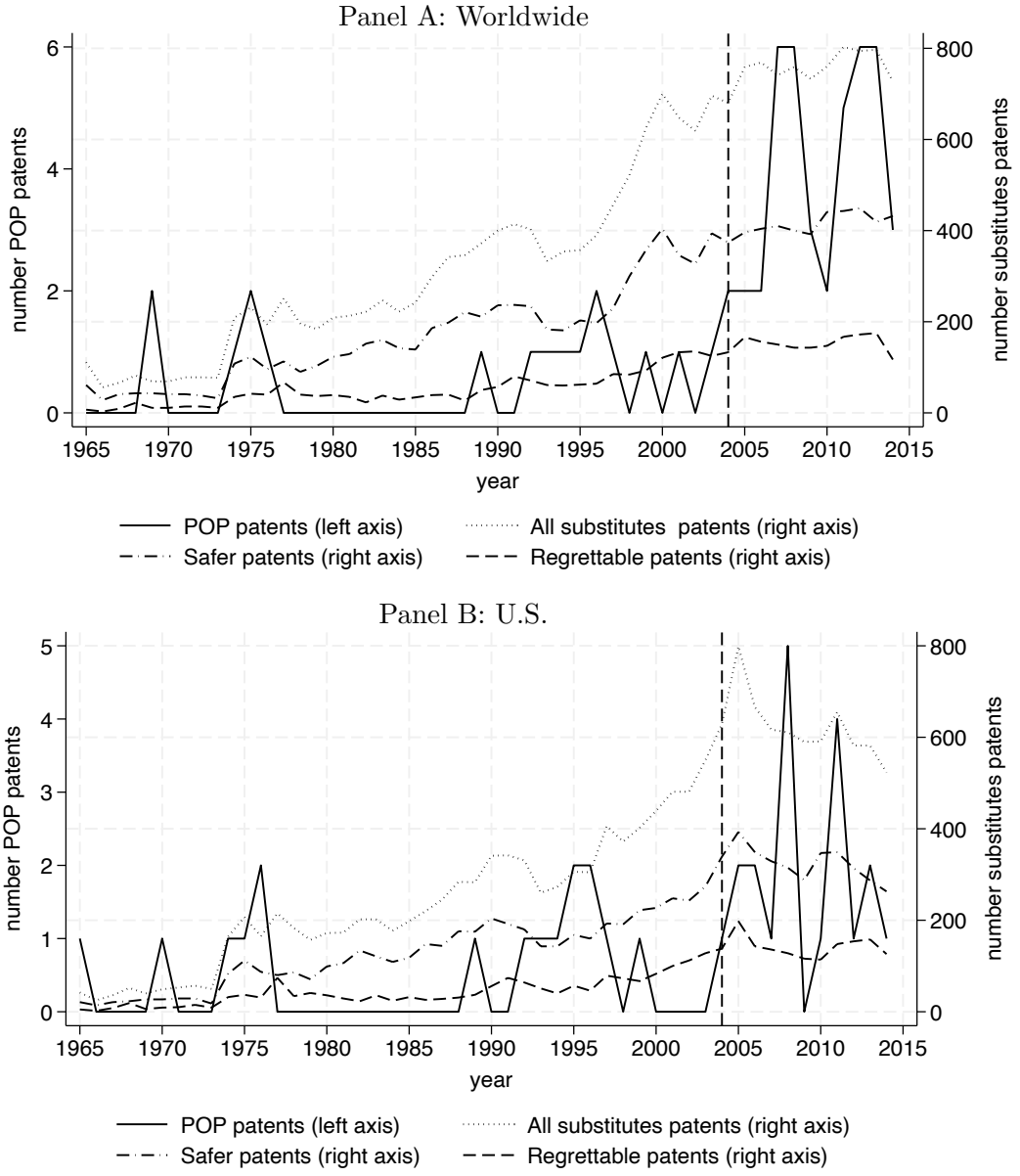
Table 3 presents the top 15 patent applicants in our dataset, ranked by patent portfolio size, which is defined as the total number of POP, regrettable, and safer patent families filed worldwide between 1965 and 2014. Notably, chemical companies seem to be active in both camps (i.e. regrettable and safer chemicals).

Table 3: Top 15 patent applicants by patent portfolio

Applicant name	all patents	POP patents	substitutes regrettable patents	substitutes safer patents
CIBA	2,469	4	401	987
THE DOW CHEMICAL	1,861	6	487	741
EXXONMOBIL	1,236	0	343	555
SUMITOMO CHEM	1,001	3	100	602
BASF	986	0	326	347
THE GOODYEAR TIRE & RUBBER	708	0	345	201
GENERAL ELECTRIC	653	0	85	352
SABIC	583	0	198	285
BAYER	522	2	120	235
SHELL OIL	479	0	42	142
DU PONT	412	17	51	239
DSM	404	0	112	170
FUJIFILM	387	0	129	76
SOLVAY	313	0	39	195
HITACHI CHEM	278	0	52	170

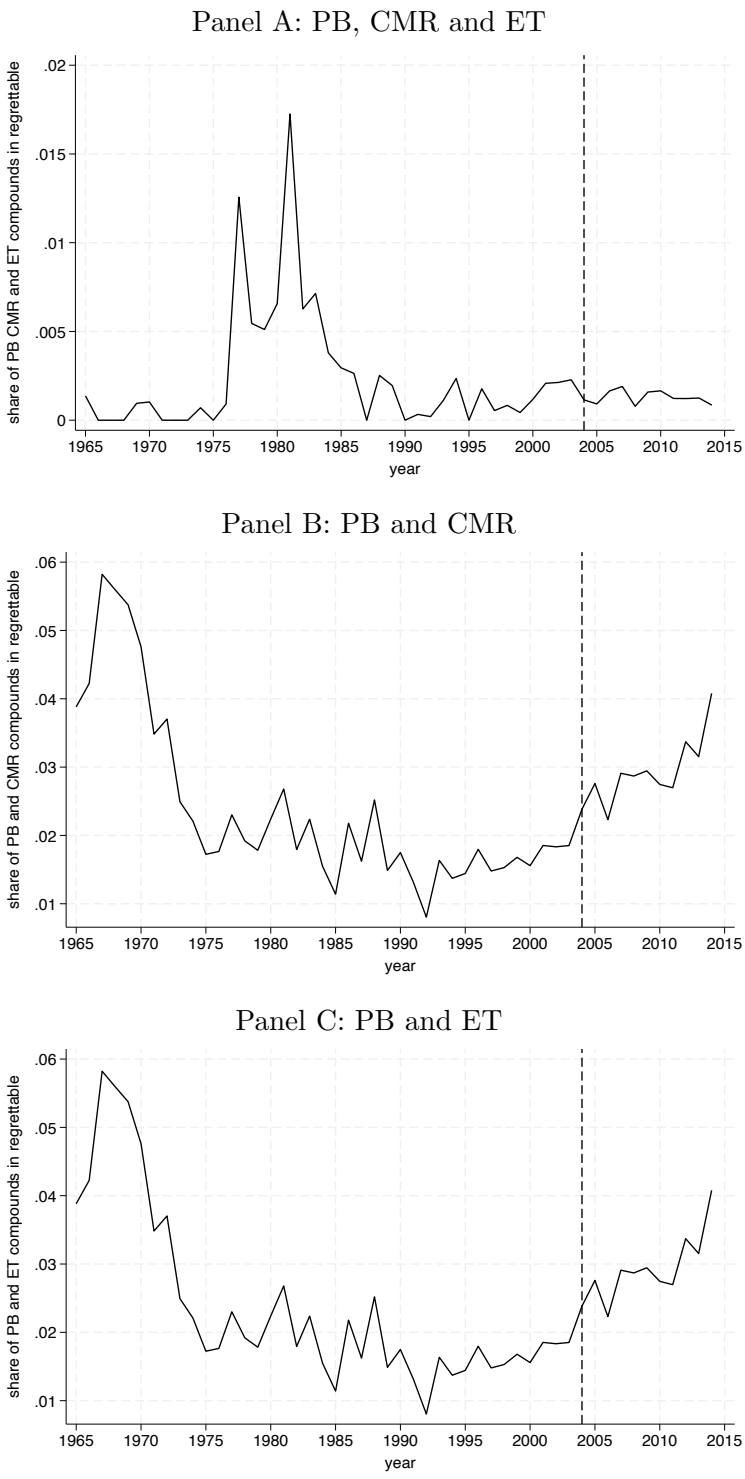
Note: The top 15 patent applicants worldwide, ranked by the size of their overall patent portfolios, are displayed along with the number of patents in each category (POP, regrettable, and safer patents). We use harmonized patent applicant names as provided in PATSTAT, which were further refined through manual cleaning. The patent portfolio represents the total number of distinct patent families filed globally between 1965 and 2014 across all analyzed chemical technologies.

Figure 2: POPs and substitute patents over time, 1965-2014



Note: The graphs illustrate the yearly number of POP and substitute patents filed worldwide (panel A) and in the U.S. (panel B). Substitute patents are identified using the ChEBI Ontology. Regrettable substitutes are those classified as both PB and CMR or PB and ET, while safer substitutes exclude compounds that are PB, CMR, or ET. The data cover the period from 1965 to 2014. The dotted line marks the year (2004) when the Stockholm Convention (SC) was ratified, leading to the banning of POPs. To avoid double counting of patent twins, only the first filing within each patent family is considered.

Figure 3: Share of POP-like compounds in regrettable patent families, 1965-2014



Note: The graphs illustrate the yearly average share of POP-like compounds present in regrettable patent families over time. Panel A plots the share of PB, CMR *and* ET compounds. Panel B plots the share of PB *and* CMR compounds. Panel C plots the share of PB *and* ET compounds. Patents filed worldwide between 1965 and 2014 are included. The dotted line marks the SC ratification year (2004). To avoid double counting of patent twins, only the first filing within each patent family is considered.

4.3 Empirical strategy

As anticipated, our goal is to assess the impact of the SC on the direction of technical change, particularly whether after the 2004 SC ratification, companies divert their R&D strategies towards safer technological alternatives. To this end, we build on previous research that tests the impact of a treaty on chemical compounds on the development of alternative technologies (Dugoua, 2023). However, unlike prior research, we do not assume alternative technologies to be "clean" by default. As discussed earlier, we use computational toxicology to classify alternatives as regrettable or safer.

A central challenge in this approach lies in identifying a credible control group—one that remains unaffected by the Convention—since spillovers between treatment and control groups would undermine a key assumption of the DID framework. To address this, we constructed a control group based on chemical ontology, composed of safer patents that exhibit similar structural and functional properties to those in the treatment group but fall within entirely distinct technological domains.[5]

This distinction is critical. By selecting patents from unrelated technological areas, we ensure that the corresponding chemicals were developed by firms for purposes other than replacing the targeted POPs. Consequently, these chemicals are unlikely to act as substitutes for the regulated substances, thereby minimizing the risk of spillovers from the treatment group to the control group.

Following this approach, the number of patent families in the resulting control group is 5,323 corresponding to 27,227 patents. Figure A1 shows that regrettable patents and their control group are associated with different technology codes.

We identify the effect of the SC using the following DID regression model:

$$\begin{aligned} Y_{k,c,p,t} = \beta_0 + \beta_1 REGRETTABLE_{k,c,p,t} + \beta_2 POST_{k,c,p} + \\ \delta_1 REGRETTABLE_{k,c,p,t} \times POST_{k,c,p} + \\ \omega_k + \eta_c + \gamma_p + \epsilon_{k,c,p,t} \end{aligned} \tag{1}$$

Our dependent variable Y is the number of ontology-based substitute patents (measured as DOCDB patent families), where k is the patent office, c is the substitute's CAS Number, p is

[5]To ensure these control patents originated from genuinely different domains, we excluded all ontology-related safe alternatives assigned to any full-digit International Patent Classification (IPC) class that included at least 10 regrettable patents.

the type of POP and t is the year of the filing of the DOCDB patent application. The dummy $REGRETTABLE_{k,c,p,t}$ equals 1 for regrettable patents, and zero for the control group. The dummy $POST_{k,c,p}$ equals 1 if patents are filed after 2004 and zero otherwise. The coefficient δ_1 of the interaction $REGRETTABLE_{k,c,p,t} \times POST_{k,c,p}$ estimates the effect of the SC treaty on inventive efforts. We include patent office fixed effects (ω_k), POP-type fixed effects (γ_p) and CAS Number fixed effects (η_c). Standard errors are clustered at the CAS Number-level.

5 Empirical results

5.1 Main results

Figure 4 shows the average inter-temporal trends of our dependent variable Y from 1965 to 2014 both worldwide (panel A) and in the U.S. (panel B). We average the number of DOCDB patent families over a five-year period to reduce the noise in the estimates. The number of safer patents in our control group is consistently lower than the number of regrettable ones over the whole period. Starting around the year of the SC, we notice a significant rise in regrettable patents which is not observable for the control group. This trend does not differ in the case of U.S. patents.

To validate the DID approach, it is essential to assume that the treated (regrettable patents) and control groups would have exhibited parallel trends in the absence of the treatment. To assess the plausibility of this assumption, we extend our baseline model (Equation 1) to estimate year-specific differences between treated and control DOCDB patent families over time, employing the following specification:

$$\begin{aligned} Y_{k,c,p,t} = \beta_0 + \beta_1 REGRETTABLE_{k,c,p,t} + \beta_2 POST_{k,c,p} + \\ \delta_1 (REGRETTABLE_{k,c,p} \times YEAR_{k,c,p,t}) + \\ \omega_k + \eta_c + \gamma_p + \epsilon_{k,c,p,t} \end{aligned} \tag{2}$$

In this equation, the year 1965 serves as the baseline omitted period. Figure 5 illustrates the estimated coefficients along with their 95% confidence intervals. The results confirm that the increase in regrettable patents did not begin before 2004, with the effect becoming especially pronounced after 2005. This finding supports the parallel trend assumption, indicating that any observed differences post-2004 are likely attributable to the Convention. This pattern is consistent also when considering U.S. patents only (see Appendix, Figure A5).

Table 4: Difference-in-difference main results

	Worldwide			U.S.
POST	0.0333	0.137	0.496	1.847
	(0.124)	(0.114)	(0.418)	(1.409)
REGRETTABLE	1.408***	1.408***	1.408***	2.513*
	(0.490)	(0.490)	(0.490)	(1.266)
POST × *REGRETTABLE*	2.743***	2.743***	2.743***	4.959***
	(0.540)	(0.540)	(0.540)	(1.227)
Observations	110,484	110,484	110,484	8,714
R-squared	0.098	0.106	0.191	0.337
Patent office FE	✓	✓	✓	-
Pop-type FE	✗	✓	✓	✓
CAS Number FE	✗	✗	✓	✓

OLS estimates of Equation 1.
Robust standard errors in parentheses, clustered by CAS Number.
Legend: *** p<0.01, ** p<0.05, * p<0.1

Table 4 presents our main DID regression results. Column 1 includes patent office fixed effects, Column 2 adds POP-type fixed effects, and Column 3 further incorporates CAS Number fixed effects. Column 4 restricts the sample to patents filed at the USPTO. Across all specifications, the interaction term ($REGRETTABLE_{k,c,p,t} \times POST_{k,c,p}$) is positive and statistically significant, indicating that regrettable patent families increased more than the control group following the SC. Quantitatively, the SC resulted in an average increase of 2.74 regrettable patent families globally, and 4.95 in the U.S., compared to the control group. When adjusted for the pre-2004 yearly averages of regrettable patent families (1.83 globally and 3.67 in the U.S.), these figures imply a 150% rise in regrettable patent families worldwide and a 135% rise in the U.S. This suggests that rather than steering innovation towards safer alternatives, the SC may have incentivized the creation of more regrettable chemical inventions.

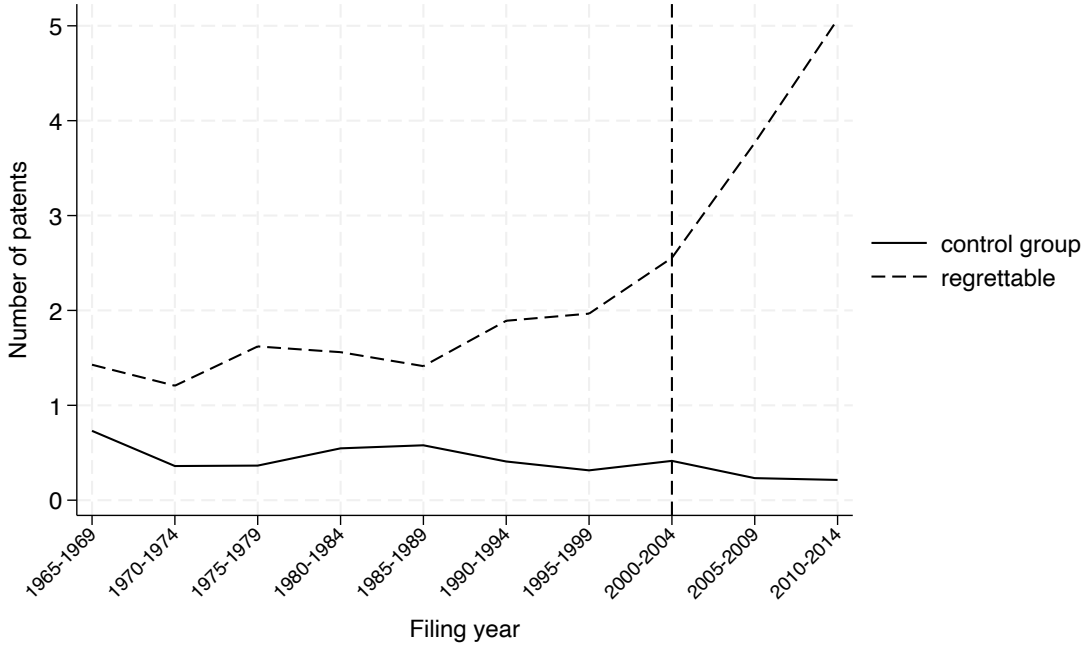
5.2 Heterogeneity across POP types

Given the potential for heterogeneous responses among different POPs to the Convention, we now examine each POP separately. We estimate our baseline model (Equation 1) using split samples for each POP. The results, presented in Table 5, reveal a positive and statistically significant coefficient for all POPs, corroborating earlier findings that the SC contributes to an increase in regrettable patents relative to safer alternatives.[6] However, when we normalize the coefficients by the average number of regrettable patent families filed prior to 2004 for

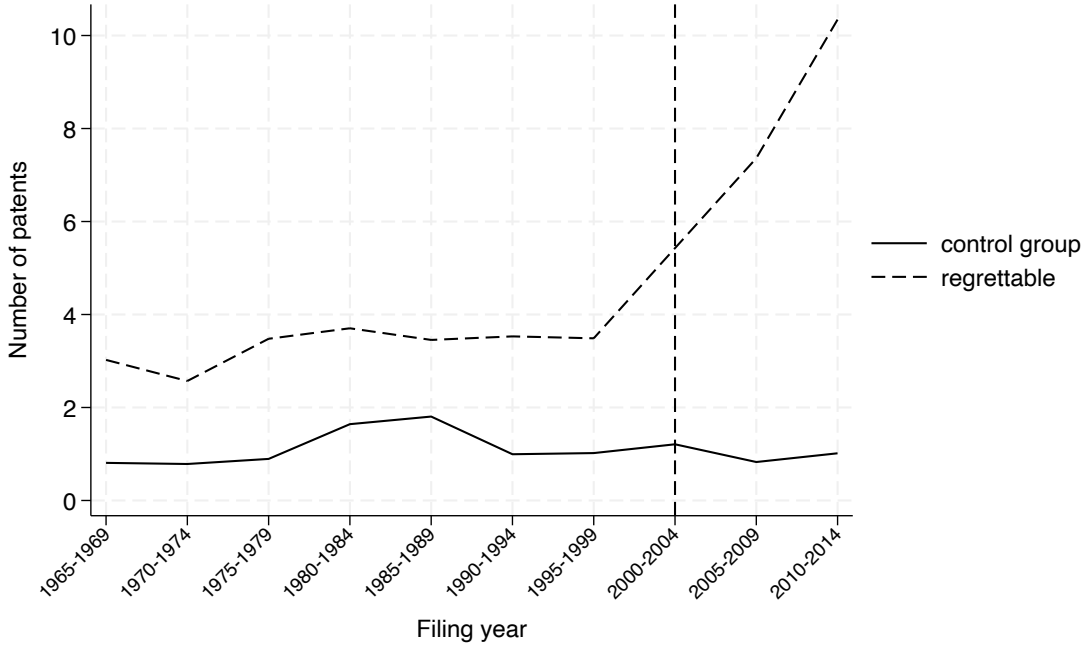
[6]Due to the limited number of observations, Toxaphene was excluded from the split sample analysis.

Figure 4: Average number of regrettable and control group patents over time

Panel A: Worldwide



Panel B: U.S.



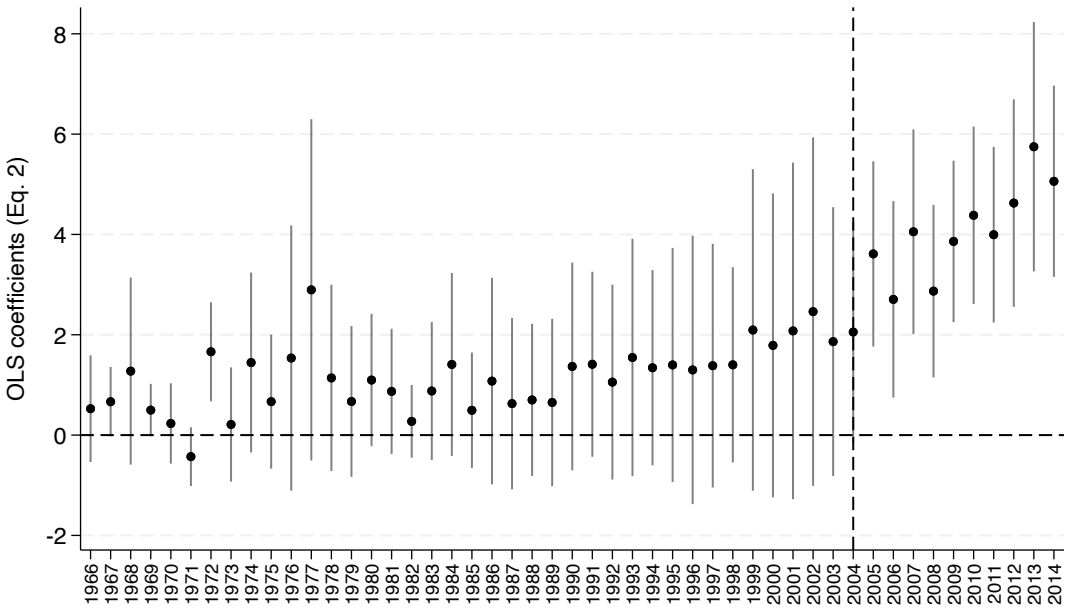
Note: Panel A plots the average number of regrettable (treated) and control group patents filed over time worldwide. Panel B plots the average number of regrettable (treated) and control group patents filed over time at the USPTO. The average number of patents is computed on a five-year period to reduce the noise in the estimates. The data cover the period 1965-2014.

Table 5: Difference-in-difference results - split sample by POP type

	Aldrin	Clordane	DDT	Dieldrin	PCDD/PCDF	Endrin	Heptachlor	Hexachlorbenzene	Mirex	PCB
POST	0.476	1.054	0.0286	0.531*	0.383	0.531*	1.054	0.239	0.794**	-0.0295
	(0.284)	(0.778)	(0.062)	(0.295)	(0.334)	(0.295)	(0.777)	(0.194)	(0.314)	(0.046)
REGRETTABLE	0.882***	1.943**	1.144***	0.890***	0.825***	0.894***	1.940**	1.064***	1.029***	0.306***
	(0.047)	(0.878)	(0.125)	(0.048)	(0.231)	(0.047)	(0.879)	(0.226)	(0.087)	(0.075)
POST × *REGRETTABLE*	3.629***	2.799***	0.624***	3.753***	0.203**	3.748***	2.802***	3.094***	3.824***	0.655***
	(0.617)	(0.464)	(0.106)	(0.602)	(0.095)	(0.602)	(0.464)	(0.543)	(0.614)	(0.106)
Observations	8,144	21,728	4,946	7,812	11,420	7,812	21,724	17,542	6,738	1,802
R-squared	0.403	0.198	0.488	0.412	0.261	0.412	0.198	0.331	0.429	0.495
CAS Number FE	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Patent office FE	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

OLS estimates of Equation 1. Split sample by POP type. Robust standard errors in parentheses, clustered by CAS Number.
All patent offices worldwide included. Legend: *** p<0.01, ** p<0.05, * p<0.1

Figure 5: Impact of the Stockholm Convention on regrettable patent families worldwide



Notes: We report OLS coefficient estimates of Equation 2 (and their 95% confidence intervals). The dependent variable is the number of patent family applications filed worldwide. The data cover the period 1965-2014.

each POP, we observe significant variation in the magnitude of the SC's impact across different POPs. The increase ranges from 401% for Dieldrin, to 12% for PCDD-PCDF, and 54% for DDT, highlighting a diverse response among the different chemicals. These differences may stem from the fact that certain POPs are exceptionally permitted for specific uses, or occur as unintentional byproducts of industrial and combustion processes (as in the case of PCDD/PCDF), thereby reducing the urgency of identifying alternatives.

Figure A6 illustrates the annual impact of the SC by POP type, based on the results of a split-sample analysis using Equation 2. In all cases, the SC has a noticeable effect on the increase of regrettable substitutes starting in 2004, with the exception of DDT (and, to some extent, PCDD-PCDF, for the reasons mentioned above). DDT represents a unique case, as shown in Figure A7, where its behavior differs depending on whether U.S. or global patents are considered. In the U.S., the number of regrettable substitutes declined after 1972, following the national ban. However, at the global level, regrettable substitutes for DDT increased after 2004, aligning with the trend observed for other POPs, although with a slight time delay. This was possibly due to the persistence of a global market for that chemical beyond the U.S.

5.3 Robustness checks

We conducted a set of robustness tests presented in Table 6.

Table 6: Difference-in-difference results - robustness checks

	1	2	3	4
	Excluding DDT	Excluding 2001-2004	Negative Binomial	Regrettable above-the-median
POST	0.513	0.504	-0.273*	0.142
	(0.430)	(0.428)	(0.142)	(0.203)
REGRETTABLE	1.418***	1.298***	1.783***	0.648***
	(0.510)	(0.420)	(0.369)	(0.080)
POST × *REGRETTABLE*	2.863***	2.853***	1.776***	2.976***
	(0.565)	(0.519)	(0.221)	(0.551)
Observations	105,538	104,410	110,484	110,484
Patent office FE	✓	✓	✓	✓
Pop-type FE	✓	✓	✓	✓
CAS Number FE	✓	✓	✓	✓

OLS estimates (Equation 1) in Columns 1, 2 and 4.
Negative Binomial estimates in Column 3.
An alternative definition of REGRETTABLE is applied in in Column 4.
All patent offices worldwide included.
Robust s.e. in parentheses, clustered by CAS Number.
Legend: *** p<0.01, ** p<0.05, * p<0.1

First, to address the observed heterogeneity across POPs and minimize potential bias in our estimates, we re-estimate Equation (1) by excluding DDT (Column 1). The results remain consistent with the main estimations (Table 4). Second, in our main analysis we define the pre- and post-treaty periods based on the year of the SC ratification (2004), rather than the year of its signature (2001). To account for potential anticipation effects, we exclude the years between 2001 and 2004 in Column 2 of Table 6. The results remain consistent. Third, to account for overdispersion, we re-run the regressions using a Negative Binomial model. Also in this case our results remain consistent (Table 6, Column 3). Finally, we test the robustness of our findings by redefining the treated group of regrettable patents. In our main analysis, patents are classified as regrettable if they contain at least one compound with PB and CMR properties; PB and ET properties; or all three—PB, CMR, and ET. This definition was chosen based on consultations with key experts, who indicated that the presence of even a single compound with POP-like properties is sufficient to signal a potentially hazardous toxicity profile. As an

alternative measure, we also classify patents as "regrettable above-the-median" if the share of PB and CMR, PB and ET, or PB, CMR, and ET compounds exceeds the median among patents that contain at least one PB, CMR, or ET compound. The results (Table 6, Column 4) remain consistent.

6 Conclusion

This paper contributes to the debate on directed technical change by examining the qualities of substitute technologies. Much of the literature defines a technology as "clean" if it eliminates a targeted ingredient—typically one under regulatory or public scrutiny. For instance, electric engines are viewed as clean alternatives to combustion engines, and biodegradable plastics as cleaner than conventional ones. Research shows that firms respond to market incentives and regulations by shifting R&D toward such alternatives (Aghion et al., 2016; Veugelers, 2012; Romagnoli, 2024; Dugoua, 2023; Budish et al., 2015; Moscona and Sastry, 2023).

From this perspective, if firms underinvest in cleaner technologies, policymakers can intervene with appropriate incentives. Yet this assumes that substitutes are truly better for the environment and society—a premise that may not always hold.

Specialized research on "regrettable" substitutes in chemistry (Zimmerman and Anastas, 2015; Blum et al., 2019) underscores the need for a more nuanced understanding of technological alternatives. Our work addresses this important gap. Focusing on the substitutes for 12 persistent organic pollutants (POPs)—among the most hazardous chemicals due to their high toxicity and persistence in the environment and human body—our study examines the impact of the 2004 ratification of the Stockholm Convention, which banned these substances globally. As expected, in line with established literature (Dugoua, 2023), the treaty spurred the development of alternative technologies.

However, our novel methodology, which combines patent analysis with computational toxicology (Biggi et al., 2022), provides a more detailed picture than previously available. We find that a significant share of "regrettable" substitutes —chemicals that, while not banned under the SC, exhibit POP-like characteristics, particularly high toxicity and persistence. Our DID analysis reveals that regrettable alternatives have increased at a much higher rate than the control group after the SC. In other words, rather than fully shifting innovation toward genuinely safer solutions, the regulatory push seems to have largely resulted in the adoption of substitutes

that remain environmentally and socially problematic.

These findings raise important theoretical questions about the underlying incentives that drive firms to favor regrettable substitutes over cleaner alternatives. This preference is central to understanding why certain policies, despite successfully phasing out harmful technologies, often fail to achieve their broader objectives— potentially paving the way for new forms of social and environmental harm. We offer two concurrent interpretations of these findings.

The first interpretation, common in the literature, relates to the path-dependent nature of knowledge accumulation in firms (David, 1994; Arthur, 1994). Knowledge develops within established technological trajectories, shaping the direction of new discoveries and making technological change largely independent of short-term economic factors like price shifts or market fluctuations (Dosi, 1982, 1997). While the directed technical change literature acknowledges path dependence in technological development (Aghion et al., 2016), it often overlooks how deeply embedded capabilities and skills—held by workers and scientists—make it difficult to shift between technological pathways (March and Simon, 1958; Nelson and Winter, 1982; Vincenti, 1990).

This challenges the assumption that firms can readily adapt to market incentives, as is sometimes suggested in models of directed technical change. In our case, the preference for regrettable substitutes may stem from structural rigidities across the R&D, production, and distribution stages of the value chain. For example, R&D scientists may be more inclined to develop variants of familiar chemicals rather than venture into entirely new—and potentially safer—alternatives. Similarly, firms may face infrastructural and logistical constraints that make it more attractive to leverage existing production facilities for developing similar chemical products rather than investing in entirely new processes. These rigidities create powerful incentives for firms to maintain existing technologies, providing an explanation for their resistance or even active lobbying against more radical shifts in their industry. This resistance often stems from the desire to protect entrenched interests and avoid the costs and uncertainties associated with significant transformation, as often implied by the chemical risk literature.

This brings us to the second interpretation which relates to how firms respond to regulations and norms. Although we know that, in general, companies comply with regulations to maintain legitimacy in the marketplace (DiMaggio and Powell, 1983), they also develop sophisticated strategies to resist, circumvent, or even shape these rules in ways that serve their own interests (Oliver, 1991). Our research suggests that the industry reacted to the SC by complying

with the letter of the law—i.e., developing alternatives to the banned chemicals—while overlooking the broader intent of the regulation, which aims to prevent the use of substances with similar harmful characteristics. This narrow approach may have allowed firms to meet formal compliance requirements without fundamentally redirecting their R&D strategies toward safer chemicals. As a result, they substitute banned chemicals with structurally similar alternatives, sidestepping the deeper regulatory objective of reducing overall toxicity and risk.

Combined with internal path dependencies that lock firms into environmentally harmful technological trajectories, strict adherence to the letter of the law offers a plausible explanation for why, despite growing normative efforts to address environmental harm, global environmental problems persist - suggesting the need to rethink policies in this domain, as we discuss towards the end of this article.

Our findings, moreover, carry significant implications for future research. Conceptually, it is crucial to re-examine R&D strategies, particularly in the early stages of technological development. Some research has suggested that once (hazardous) products enter the market, their use and diffusion are embedded within broader socio-technical systems (Geels, 2004), consisting of a complex architecture of relationships and actors (e.g. industry, regulators, workers, unions, users, etc.) that shape meanings, values, and practices, making the resulting socio-technical structures deeply entrenched and difficult to reverse. Innovation scholars have sometimes regarded this process as "irreversible", meaning that "the artefact or the system cannot be easily dismantled after it has been put together", else said, "irreversibility, once achieved, is what makes a technology... a structural factor itself." (Rip and Kemp, 1998, p. 340). As a result, fixing the problem after its occurrence is very costly to the point where it is almost impossible. Hence we think that an area for future research is the understanding of the factors shaping the direction of technological progress before innovations reach the market—specifically, during the early stages of development.

Methodologically, our works highlight the need to move beyond simplistic definitions of clean or green technological alternatives. The chemical industry provides a particularly useful case, as it allows for a precise measurement of alternatives based on toxicity and other sustainability metrics (Biggi et al., 2022). However, the broader lesson extends beyond chemicals: current approaches often rely on overly rigid, one-dimensional distinctions between "dirty" and "clean" technologies. A different measurement approach is needed—one that accounts for the multi-dimensional nature of the harm caused by substitute technologies across different industries

and recognizes that not all so-called cleaner alternatives deliver meaningful environmental and societal benefits. A closer inspection of the substitute technologies is crucial to understanding the effectiveness of incentives set to replace dirty technologies with superior ones.

Finally, this research has important policy implications. If regulatory or market incentives eliminate one problem but create the conditions for a new generation of equally harmful ones—as observed in this study—then relying on market forces alone to "weed out the 'bad' innovations" (Coad et al., 2021, p. 103) is a flawed approach. Effective regulation cannot focus narrowly on individual hazards; it must consider the broader incentive structures shaping technological choices to prevent so-called solutions from introducing new risks for human health or the environment. The literature on directed technical change acknowledges that "the direction of technology can be systematically distorted" (Acemoglu, 2023, p. 2). However, it largely assumes that firms will correct these distortions in response to market incentives, while governments need only design the right policy levers. The problem is that firms, left to their own devices, may opt for solutions that are privately optimal but socially suboptimal—particularly in cases of regrettable substitutions. If the goal is to drive innovation toward genuinely safer and more sustainable alternatives, then policymakers must take a more active role in shaping not just the rate but also the direction of technological change, by promoting informed assessments well before a technology becomes irreversibly entrenched in the market (Geels, 2004). Some scholars talk about democratising innovation by "opening up democratic practice around directionality in science and technology" (Stirling, 2024, p. 16) and bringing policymaking in this field to a new level, where we can effectively achieve the goal of a more sustainable future. We think this study provides additional empirical support to motivate the experimentation of these novel policy approaches.

References

Acemoglu, D. (2002): "Directed technical change," *The Review of Economic Studies*, 69, 781–809.

——— (2023): "Distorted innovation: does the market get the direction of technology right?" in *AEA Papers and Proceedings*, American Economic Association 2014 Broadway, Suite 305, Nashville, TN 37203, vol. 113, 1–28.

Aghion, P., A. Dechezleprêtre, D. Hemous, R. Martin, and J. Van Reenen (2016): "Carbon taxes, path dependency, and directed technical change: Evidence from the auto industry," *Journal of Political Economy*, 124, 1–51.

Arrow, K. J. (1962): "The economic implications of learning by doing," *The Review of Economic Studies*, 29, 155–173.

Arthur, W. B. (1994): *Increasing returns and path dependence in the economy*, University of michigan Press.

——— (2009): *The nature of technology: What it is and how it evolves*, New York Free Press.

Attina, T. M., R. Hauser, S. Sathyanarayana, P. A. Hunt, J.-P. Bourguignon, J. P. Myers, J. DiGangi, R. T. Zoeller, and L. Trasande (2016): "Exposure to endocrine-disrupting chemicals in the USA: a population-based disease burden and cost analysis," *The Lancet Diabetes & Endocrinology*, 4, 996–1003.

Benfenati, E., S. Pardoe, T. Martin, R. G. Diaza, A. Lombardo, A. Manganaro, and A. Gissi (2013): "Using toxicological evidence from QSAR models in practice," *ALTEX-Alternatives to animal experimentation*, 30, 19–40.

Biggi, G., E. Giuliani, A. Martinelli, and E. Benfenati (2022): "Patent toxicity," *Research Policy*, 51, 104329.

Biggi, G., E. Giuliani, A. Martinelli, and A. Parenti (2024): "Path dependency, social capital and the geography of dirty inventions," *Industry and Innovation*, 1–25.

Blum, A., M. Behl, L. S. Birnbaum, M. L. Diamond, A. Phillips, V. Singla, N. S. Sipes, H. M. Stapleton, and M. Venier (2019): "Organophosphate ester flame retar-

dants: are they a regrettable substitution for polybrominated diphenyl ethers?" *Environmental Science & Technology Letters*, 6, 638–649.

Budish, E., B. N. Roin, and H. Williams (2015): "Do firms underinvest in long-term research? Evidence from cancer clinical trials," *American Economic Review*, 105, 2044–2085.

Buñay, J., M. Kossai, C. Damon-Soubeyrant, A. De Haze, J.-P. Saru, A. Trousson, C. de Joussineau, E. Bouchareb, A. Kocer, and M. Vialat (2023): "Persistent organic pollutants promote aggressiveness in prostate cancer," *Oncogene*, 42, 2854–2867.

CAS-Scifinder (2024): "Quick reference guide," Tech. rep., American Chemical Society, https://web.cas.org/marketing/solutions/sfdp/scifinder/SCIGENENGREF101245-SciFinder-Quick-Reference-Guide-Commercial-A4.pdf.

Castaldi, C., E. Giuliani, M. Kyle, and A. Nuvolari (2024): "Are intellectual property rights working for society ?" *Research Policy*, 53, 104936.

Cherkasov, A., E. N. Muratov, D. Fourches, A. Varnek, I. I. Baskin, M. Cronin, J. Dearden, P. Gramatica, Y. C. Martin, R. Todeschini, et al. (2014): "QSAR modeling: where have you been? Where are you going to?" *Journal of medicinal chemistry*, 57, 4977–5010.

Coad, A., G. Biggi, and E. Giuliani (2021): "Asbestos, leaded petrol, and other aberrations: comparing countries' regulatory responses to disapproved products and technologies," *Industry and Innovation*, 28, 201–233.

David, P. A. (1994): "Why are institutions the 'carriers of history'?: Path dependence and the evolution of conventions, organizations and institutions," *Structural Change and Economic Dynamics*, 5, 205–220.

de Boer, J., I. van der Veen, and H. Fiedler (2022): "Global interlaboratory assessments on PCBs, organochlorine pesticides and brominated flame retardants in various environmental matrices 2017/2019," *Chemosphere*, 295, 133991.

Dechezleprêtre, A., R.-P. Märtin, and M. Mohnen (2014): "Knowledge spillovers from clean and dirty technologies," *Centre for Economic Performance*.

DiMaggio, P. J. and W. W. Powell (1983): "The iron cage revisited: Institutional isomorphism and collective rationality in organizational fields," *American sociological review*, 48, 147–160.

Dosi, G. (1982): "Technological paradigms and technological trajectories: a suggested interpretation of the determinants and directions of technical change," *Research policy*, 11, 147–162.

——— (1997): "Opportunities, incentives and the collective patterns of technological change," *The Economic Journal*, 107, 1530–1547.

Dugoua, E. (2023): "Induced innovation and international environmental agreements: evidence from the ozone regime," *Review of Economics and Statistics*, 1–45.

Dugoua, E. and T. Gerarden (2023): "Induced innovation, inventors, and the energy transition," Working Paper 31714, National Bureau of Economic Research.

Eurostat (2024): "Chemicals production and consumption statistics," Tech. rep., Eurostat Statistics Explained.

Fuadah, Y. N., M. A. Pramudito, L. Firdaus, F. J. Vanheusden, and K. M. Lim (2024): "QSAR Classification Modeling Using Machine Learning with a Consensus-Based Approach for Multivariate Chemical Hazard End Points," *ACS omega*, 9, 50796–50808.

Geels, F. W. (2004): "From sectoral systems of innovation to socio-technical systems: Insights about dynamics and change from sociology and institutional theory," *Research Policy*, 33, 897–920.

Haghani, M., H. Ghaderi, and D. Hensher (2024): "Hidden effects and externalities of electric vehicles," *Energy Policy*, 194, 114335.

Hicks, J. R. (1932): "Marginal productivity and the principle of variation," *Economica*, 79–88.

Holder, J. W. (1986): *The Assessment of the Carcinogenicity of Dicofol (Kelthane [TM]), DDT, DDE, and DDD (TDE)*, Office of Health and Environmental Assessment, Office of Research and Development, US Environmental Protection Agency.

Jayaraj, S. and M. Gittelman (2018): "Impact of scientific maps on technological search and novelty," in *Academy of Management Proceedings*, 1, 15414.

Kaushal, S. S., K. L. Wood, J. G. Galella, A. M. Gion, S. Haq, P. J. Goodling, K. A. Haviland, J. E. Reimer, C. J. Morel, B. Wessel, et al. (2020): "Making 'chemical cocktails'–Evolution of urban geochemical processes across the periodic table of elements," *Applied Geochemistry*, 119, 104632.

Lane, M. M., E. Gamage, S. Du, D. N. Ashtree, A. J. McGuinness, S. Gauci, P. Baker, M. Lawrence, C. M. Rebholz, and B. Srour (2024): "Ultra-processed food exposure and adverse health outcomes: umbrella review of epidemiological meta-analyses," *The BMJ*, 384.

March, J. and H. Simon (1958): *Organizations*, Cambridge, MA: Blackwell.

Moscona, J. and K. A. Sastry (2023): "Does directed innovation mitigate climate damage? Evidence from US agriculture," *The Quarterly Journal of Economics*, 138, 637–701.

Nelson, R. R. and S. Winter (1982): *An evolutionary theory of economic change*, Harvard University Press.

Oliver, C. (1991): "Strategic responses to institutional processes," *Academy of management review*, 16, 145–179.

Pore, S., A. Pelloux, A. Bergqvist, M. Chatterjee, and K. Roy (2025): "Intelligent consensus-based predictions of early life stage toxicity in fish tested in compliance with OECD Test Guideline 210," *Aquatic Toxicology*, 279, 107216.

Rip, A. and R. Kemp (1998): "Technological change," in *Human choice and climate change: Vol. II, Resources and Technology*, Battelle Press, 327–399.

Romagnoli, M. (2024): "Clean sweep: Electricity liberalization and the direction of technological change in the electricity sector," *Research Policy*, 53, 105055.

Stirling, A. (2024): "Responsibility and the hidden politics of directionality: opening up 'innovation democracies' for sustainability transformations," *Journal of Responsible Innovation*, 11, 2370082.

Trasande, L. (2017): "Exploring regrettable substitution: replacements for bisphenol A," *The Lancet Planetary Health*, 1, e88–e89.

Van den Berg, H. (2009): "Global status of DDT and its alternatives for use in vector control to prevent disease," *Environmental Health Perspectives*, 117, 1656–1663.

Van Noorden, R. (2018): "Software improves toxicity tests," *Nature*, 559, 163–163.

Veugelers, R. (2012): "Which policy instruments to induce clean innovating?" *Research Policy*, 41, 1770–1778.

Vincenti, W. G. (1990): *What Engineers Know, and How They Know It*, Johns Hopkins University Press.

Zakharov, A. V., T. Zhao, D.-T. Nguyen, T. Peryea, T. Sheils, A. Yasgar, R. Huang, N. Southall, and A. Simeonov (2019): "Novel consensus architecture to improve performance of large-scale multitask deep learning QSAR models," *Journal of chemical information and modeling*, 59, 4613–4624.

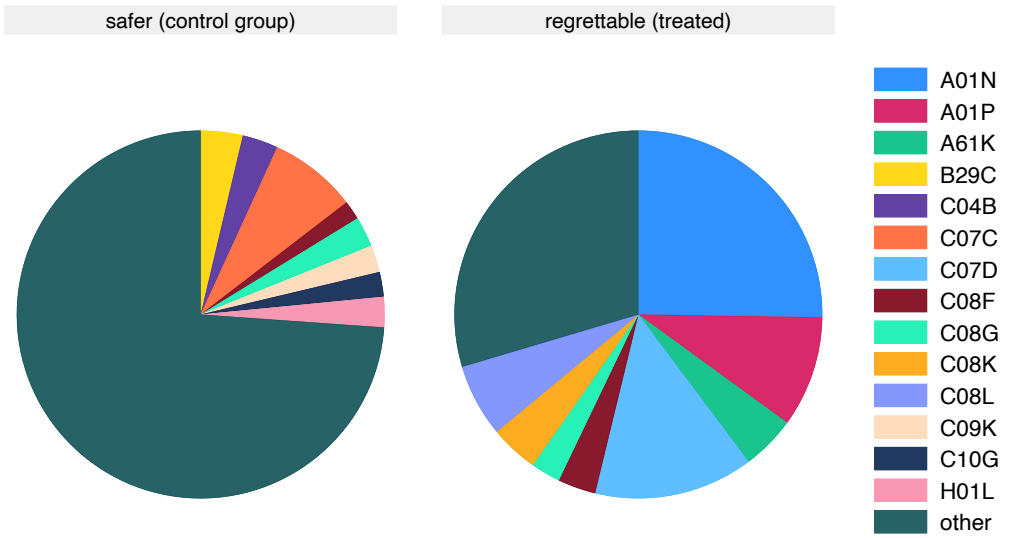
Zimmerman, J. B. and P. T. Anastas (2015): "Toward designing safer chemicals," *Science*, 347, 215–215.

Zimmerman, J. B., P. T. Anastas, H. C. Erythropel, and W. Leitner (2020): "Designing for a green chemistry future," *Science*, 367, 397–400.

Zuccarello, P., G. O. Conti, F. Cavallaro, C. Copat, A. Cristaldi, M. Fiore, and M. Ferrante (2018): "Implication of dietary phthalates in breast cancer. A systematic review," *Food and Chemical Toxicology*, 118, 667–674.

A Appendix: Tables and figures

Figure A1: Patent IPC codes: treated vs. control group



Note: The figure indicates that the safer patents selected as the control group belong to different technological classes than regrettable patents, reflecting their distinct industrial applications. The patent codes follow the International Patent Classification (IPC) system.

Figure A2: Substitutes' CAS Number

POP	Substitute CAS Number
Aldrin	465-73-6; 4971-48-6; 39765-80-5; 12408-14-9; 24009-05-0; 1024-57-3
Chlordane	128-10-9; 13051-18-8; 60-57-1; 72-20-8; 848942-61-0; 27304-13-8; 2550-75-6; 39765-80-5; 12408-14-9; 24009-05-0
Dichlorodiphenyltrichloroethane (DDT)	2550-75-6; 465-73-6; 4971-48-6; 297-78-9; 30600-22-7; 20622-81-5; 25038-78-2; 275363-11-6; 77-73-6; 1715-40-8; 115-29-7; 202138-50-9; 33213-65-9; 8003-45-0; 959-98-8; 1024-57-3; 27304-13-8
Dieldrin	106128-91-0; 1954-28-5; 72-54-8
Heptachlor	164203-73-0; 337376-15-5; 53-19-0; 2642-80-0; 2971-22-4; 2387-16-8; 27430-80-4; 115-32-2; 77008-62-9; 56961-47-8
Hexachlorobenzene	124042-17-7; 2971-36-0; 101-76-8; 134-83-8; 25249-39-2; 617-63-0; 68679-99-2; 71216-00-7; 72-55-9; 2642-82-2; 3424-82-6; 5339-67-3; 92291-62-8; 128-10-9; 13051-18-8; 60-57-1; 72-20-8; 848942-61-0; 1024-57-3; 27304-13-8; 465-73-6; 4971-48-6; 39765-80-5; 12408-14-9; 24009-05-0; 2550-75-6; 20622-81-5; 25038-78-2; 275363-11-6; 77-73-6; 297-78-9; 30600-22-7; 1715-40-8; 115-29-7; 202138-50-9; 33213-65-9; 8003-45-0
Mirex	959-98-8; 12408-10-5; 13280-72-3
Toxaphene	634-66-2
Polychlorinated biphenyls (PCB)	63697-20-1; 634-90-2; 63697-21-2; 12408-10-5; 63697-22-3; 95-94-3; 120-82-1; 12214-13-0; 63697-18-7; 1061747-72-5; 12002-48-1; 51703-47-0; 818-26-8; 87-61-6; 93714-04-6; 2199-69-1; 24634-92-2; 25321-22-6; 95-50-1; 608-93-5; 541-73-1; 63697-17-6; 106-46-7; 55232-43-4; 71856-02-5; 73513-56-1; 108-70-3; 63697-19-8; 64369-13-7; 27134-27-6; 608-27-5; 95-76-1; 95-77-2; 95-73-8; 106-43-4; 1076-28-4; 3327-51-3; 108-90-7; 3114-55-4; 542-18-7; 68411-45-0; 935-95-5; 25167-83-3; 4901-51-3; 12698-64-5; 58-90-2; 60583-65-5; 29764-02-1; 87-87-6; 101802-54-4; 131-52-2; 6338-69-8; 73927-19-2; 87-86-5; 608-94-6; 62641-66-1; 77001-45-7; 95-95-4; 13330-18-2; 626-43-7; 15470-55-0; 95-82-9; 25185-95-9; 51225-19-5; 608-31-1; 591-35-5
PCDD/PCDF	609-20-1; 141-85-5; 14338-36-4; 1198-55-6; 94744-26-0; 25167-85-5; 3978-67-4; 32139-72-3; 32139-72-3; 824-69-1; 87079-96-7; 20103-10-0; 20513-80-8; 52166-72-0; 583-78-8; 71066-28-9; 1404437-62-2; 1452-94-4; 87-65-0; 93720-92-4; 25167-82-2; 68359-37-5; 88-06-2; 120-83-2; 25167-81-1

Figure A3: Toxicity predictions. Criteria for classification

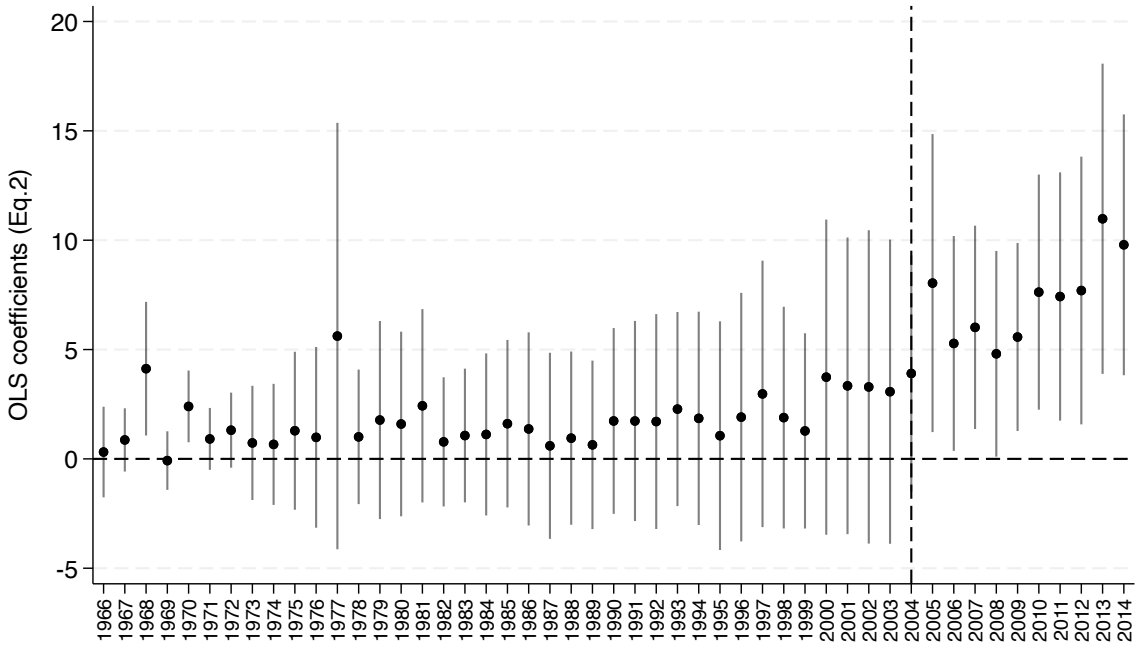
Toxicity class	Toxicity endpoint	QSAR models	Scale of possible results	Criteria for classification
PB (Persistent or Bioaccumulative)	Persistence	IRFMN (Soil, Sediments, Water)	nP (not persistent); P (persistent); vP (very persistent)	Prediction = 'P', 'vP' + Good reliability (in one or more QSAR model)
	Bioaccumulation	KNN, Meylan, Arnot-Gobas	Toxicity expressed in log(Kow)	Prediction >= 3.3 log(Kow) + Good reliability (in one or more QSAR model)
	Ready Biodegradability	IRFMN	Readily Biodegradable; Possible Readily Biodegradable; NON-Readily Biodegradable; Not classifiable	Prediction = 'NON-Readily Biodegradable', 'Possible NON-Readily Biodegradable' + Good reliability (in one or more QSAR model)
CMR (Carcinogenic, Mutagenic, and Toxic for Reproduction)	Carcinogenicity	CAESAR, ISS, IRFMN/ANTARES, INSACC-CGX, IRFMN CONSENSUS	Carcinogen; NON-Carcinogen	Prediction = 'Carcinogen' + Good reliability (in one or more QSAR)
	Mutagenicity	(CAESAR, ISS, SARpy, KNN)	Mutagenic; NON-Mutagenic	Prediction = 'Mutagenic' + Consensus score >0.5
	Reproductive toxicity	P&G, CAESAR	Toxicant; NON-Toxicant	Prediction = 'Toxicant' + Good reliability (in one or more QSAR)
ET (Ecotoxic)	Fish toxicity	SARpy/IRFMN	Toxic-1 (<1 µg/L); Toxic-2 (1-10 µg/L); Toxic-3 (10-100 µg/L); NON-Toxic (>100 µg/L)	Prediction = 'Toxic-1' (<1 µg/L); 'Toxic-2' (1-10 µg/L); 'Toxic-3' (10-100 µg/L) + Good reliability
	Daphnia Magna toxicity	EPA, DEMETRA, IRFMN, COMBASE	Toxicity expressed in mg/L	Prediction >=1 mg/L + Good reliability
	Algae toxicity	COMBASE	Toxic; NON-Toxic	Prediction = 'Toxic' + Good reliability

Source: Biggi et al. (2022)

Figure A4: Frequency of patent files by the different patent offices

Patent Office	Freq.	Percent	Cum.
US	15,820	19.62	19.62
EP	9,656	11.97	31.59
JP	7,585	9.41	41
CN	6,111	7.58	48.58
DE	5,606	6.95	55.53
CA	4,647	5.76	61.29
KR	4,444	5.51	66.8
AU	2,905	3.6	70.4
TW	2,805	3.48	73.88
BR	2,702	3.35	77.23
ES	2,318	2.87	80.1
AT	1,986	2.46	82.56
MX	1,373	1.7	84.26
GB	1,269	1.57	85.83
FR	1,214	1.51	87.34
RU	751	0.93	88.27
ZA	734	0.91	89.18
PL	603	0.75	89.93
IT	583	0.72	90.65
DK	573	0.71	91.36
NL	570	0.71	92.07
MY	478	0.59	92.66
NO	433	0.54	93.2
AR	382	0.47	93.67
BE	320	0.4	94.07
SG	302	0.37	94.44
NZ	297	0.37	94.81
IL	281	0.35	95.16
HK	273	0.34	95.5
FI	250	0.31	95.81
PT	248	0.31	96.12
SE	222	0.28	96.4
HU	219	0.27	96.67
IB	192	0.24	96.91
CH	174	0.22	97.13
IN	171	0.21	97.34
CZ	164	0.2	97.54
EA	146	0.18	97.72
CO	127	0.16	97.88
CL	114	0.14	98.02
SU	110	0.14	98.16
SK	104	0.13	98.29
DD	94	0.12	98.41
TR	92	0.11	98.52
ID	87	0.11	98.63
CS	86	0.11	98.74
UA	80	0.1	98.84
GR	76	0.09	98.93
Others	871	0.1	100
Total	80,648	100	100

Figure A5: Impact of the Stockholm Convention on regrettable inventions in the U.S.



Notes: OLS coefficient estimates of Equation 2 (and their 95% confidence intervals) are reported. The dependent variable is the number of patent applications filed in the U.S. The data cover the period 1965-2014.

Figure A6: Impact of the Stockholm Convention across POPs substitutes

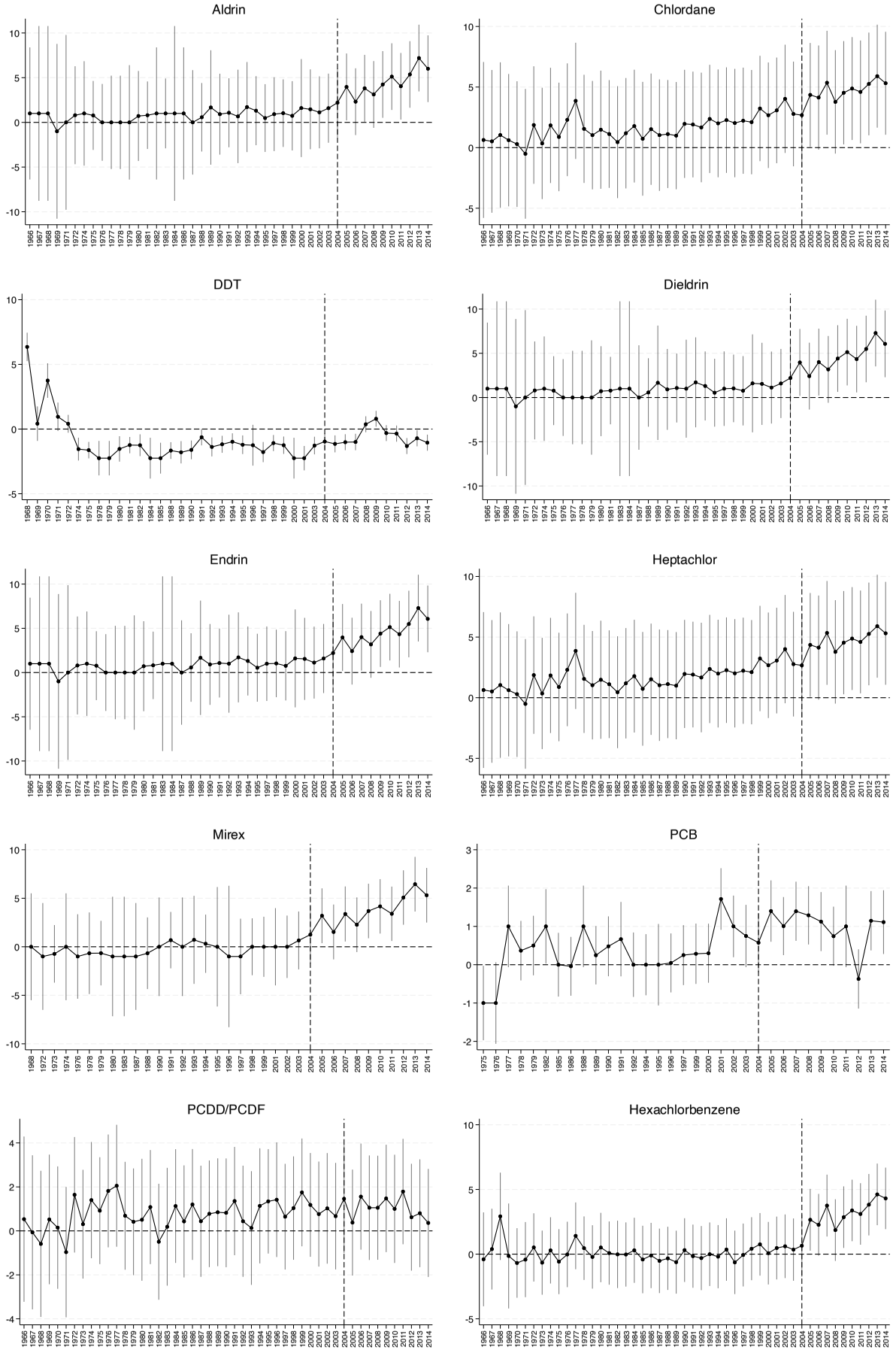


Figure A7: Impact of the Stockholm Convention on DDT substitute patents - U.S.

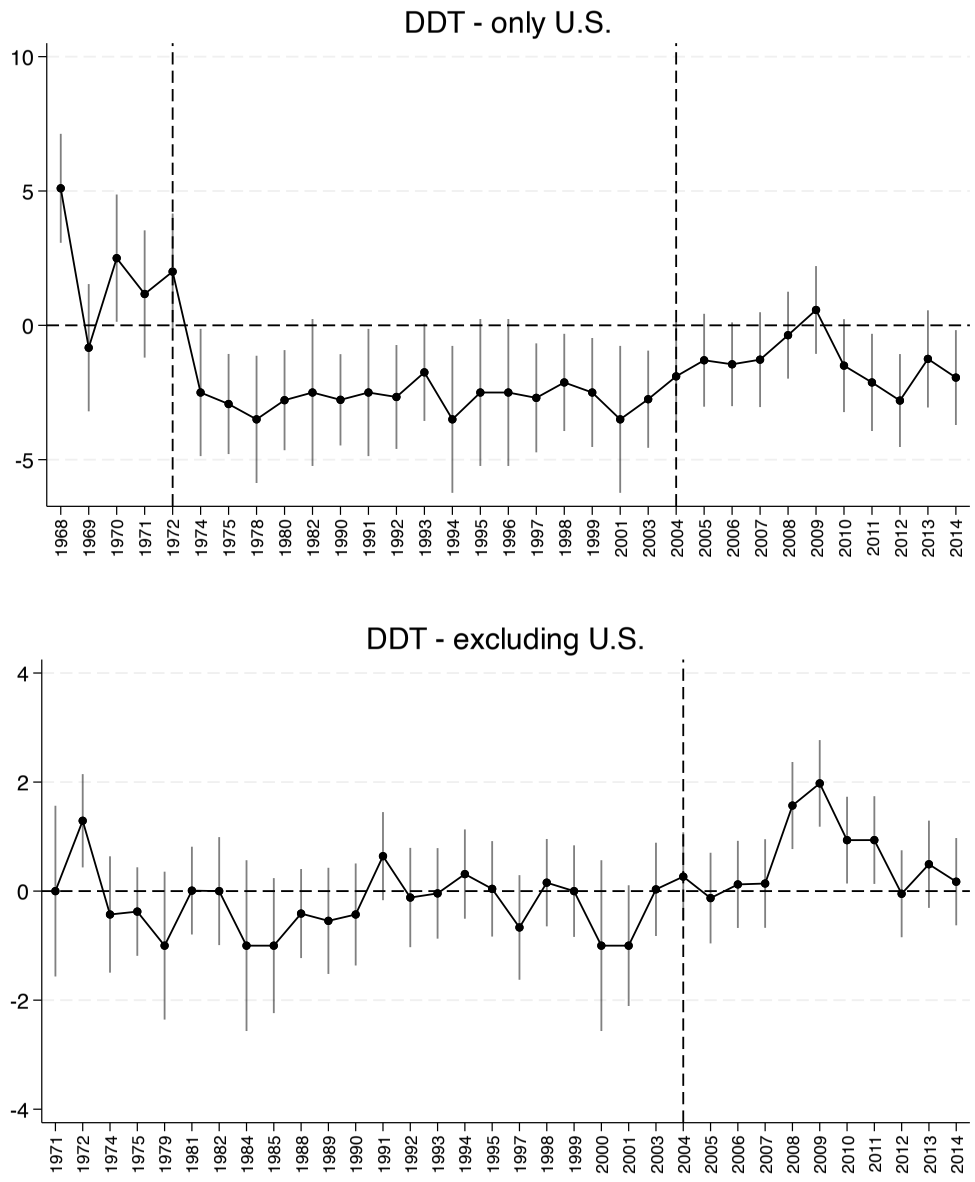
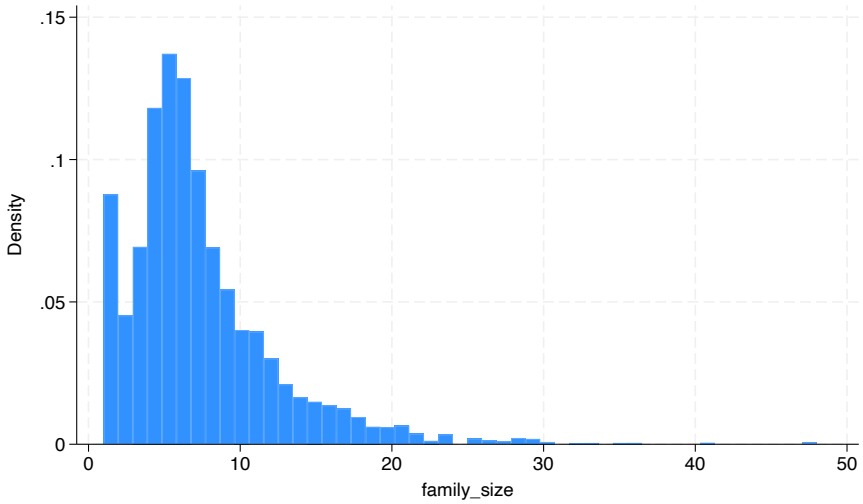


Figure A8: Distribution of patent family size



Note: The figure presents the distribution of DOCDB family sizes for POP and substitute patents filed between 1965 and 2014.