Directed Technical Change:

When Substitution Leads to Regret

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Abstract

We study the impact of the 2004 Stockholm Convention, which globally banned twelve highly toxic persistent organic pollutants (POPs), on chemical innovation. By combining patent data with computational chemistry measures of toxicity and environmental persistence, we analyze the properties of patented compounds. We find no evidence that the ban stimulated innovation toward safer alternatives. Instead, it increased patenting of substitute compounds that display POP-like characteristics, including high toxicity and persistence, despite not being covered by the ban. These results indicate that environmental regulation may redirect innovation toward formally compliant but equally dangerous technologies.

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).

Building on early insights on induced innovation and relative factor incentives (Hicks, 1932), 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 (DTC) (Acemoglu, 2002). 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 (Acemoglu, 2023). 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 (e.g., Jaffe and Palmer, 1997; Popp, 2002; Calel and Dechezleprêtre, 2016; Dugoua, 2025; Dugoua and Gerarden, 2025).

We argue that a weak point of the DTC empirical 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 in no way diminishes the importance of R&D investment in alternative technologies; rather, it underscores that the current framework — by overlooking these additional dimensions — provides an incomplete picture of how technological change, and its directional nature, respond to policy.

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. We identify three mechanisms underlying this result: technological path dependence, with regrettable patents closely resembling banned POPs more than safer substitutes; country-level economic and institutional incentives that amplify regrettable substitution where pressures to replace POPs are strongest and the country's general environmental orientation is weaker. Instead, no evidence is found that the effect is driven by a lack of prior scientific knowledge of substitute chemicals' toxicity.

Our findings 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 and 6 present the empirical results and the underlying mechanisms, and Section 7 concludes with a discussion of key findings and implications.

2 Background literature and gaps

Within the Directed Technical Change (DTC) framework (Acemoglu, 1998, 2002, 2023), inventive effort responds endogenously to relative profitability and policy signals, potentially steering R&D toward socially desirable trajectories (Acemoglu et al., 2012). When signals are weak or distorted, markets may deliver misdirected innovation (Acemoglu, 2023).

This theoretical framework has been subjected to extensive empirical scrutiny (for a review see Dechezleprêtre and Sato, 2017). Early evidence shows that environmental policy pressures direct innovation toward cleaner technologies by prompting firms to increase overall R&D (Jaffe and Palmer, 1997) and by stimulating environmental patenting (Lanjouw and Mody, 1996; Brunnermeier and Cohen, 2003). Shifting the focus from regulatory pressure to market-based incentives, Popp (2002) examines how changes in relative input prices alter firms' incentives to develop more energy-efficient technologies—an empirical test closely aligned with Hicks (1932)'s induced-innovation mechanism.

More recent studies provide sharper empirical identification of these effects. Calel and Dechezleprêtre (2016) show that inclusion in the EU Emissions Trading System increased low-carbon patenting by regulated firms, without crowding out innovation in other technological areas. In the automotive industry, Aghion et al. (2016) find that higher fuel prices and tighter standards redirect R&D toward cleaner powertrains and document persistent, path-dependent effects driven by firms' accumulated technological capabilities - consistent with evolutionary theories of technical change (Nelson and Winter, 1982; Dosi, 1982) and technological lock-in (Arthur, 1994; David, 1994).

Other studies emphasize the importance of environmental policy design (for an overview, see Kemp and Pontoglio, 2011; Popp, 2019). What matters is not merely the existence of regulation, but how it is crafted across dimensions such as the nature of the policy - e.g., market-based instruments versus targeted subsidies (Johnstone et al., 2010) - its stringency and credibility (Rogge and Reichardt, 2016), monitoring and enforcement mechanisms, and its interaction with other policy instruments, particularly innovation policies (Veugelers, 2012; Fabrizi et al., 2018).

In the context of international cooperation, Dugoua (2025) provides the first causal evidence

that global environmental agreements can induce innovation within chemistry: the Montreal Protocol triggered a 400–500% post-1987 increase in substitutes for ozone-depleting substances. Complementary evidence from Finus and Tjøtta (2003) and Dekker et al. (2012) indicates that transboundary pollution protocols similarly induced compliance innovation and technology adoption among signatories.

While there is strong evidence that environmental policy can steer innovation, most studies operationalize directionality through a clean–dirty dichotomy. This simple categorization is a limitation as it implicitly assumes that technologies eliminating the contested source of harm are unambiguously superior, cleaner alternatives. By focusing on a single contested dimension of the technology's impact, this approach tends to ignore potential other side effects or sustainability challenges that may emerge from the allegedly cleaner alternative. Also, ambiguity about the environmental impact of new technologies poses significant concerns, as extant policies or incentives may foster steady cycles of regrettable substitutions, potentially undermining long-term sustainability goals. These elements of concern are little considered in the existing DTC literature, which may thus be overly optimistic about the power of incentives and regulatory action to fix past problems and steer innovation in the "right" direction.

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).

Our study extends the empirical scope of DTC by documenting the risks embedded in technological substitutes and showing how environmental regulation may redirect innovation toward new, yet undesirable, alternatives. Treating all post-regulation substitutes as inherently superior obscures firms' strategic responses to policy. Absent a clear distinction between genuinely cleaner technologies and regrettable substitutes, it is impossible to assess whether regulation induces truly transformative innovation or merely reallocates inventive effort toward formally

compliant but substantively similar technologies.

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 and entered into force in 2004 through ratification. The treaty aimed to eliminate or severely restrict the "dirty dozen" POPs and provided mechanisms for international cooperation and support for developing nations. It entered into force on May 17, 2004 (our treatment year), and expanded to include additional harmful chemicals over time. While individual countries have implemented varied regulations to address these pollutants, such country-level measures are inherently limited in scope. They restrict use domestically, but do little to influence global innovation behavior, as companies typically develop products and technologies with international markets in mind. In contrast, the Stockholm Convention—ratified by 110 parties worldwide—represents a coordinated and comprehensive regulatory effort. Its broad international reach makes it a significantly more impactful and meaningful regulatory shock, capable of influencing both market access and the direction of inventive activity on a global scale.

To sum up, 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 encouraged the proliferation of regrettable alternatives, rather than safer ones.

4 Methodology

The 2004 entry into force 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 from the Chemical Abstract Society (CAS), 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 novel computational chemistry methods, allowing us to distinguish between patents containing regrettable substitutes (regrettable patents) and safer patents. In our empirical strategy, we employ a standard DID approach, using as a control group a selected group of safer patents that are not likely to be 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, 2025). Chemical patents have two advantages. First, molecules can be precisely traced in patent records, enabling the identification of the chemical characteristics of compounds for which assignees seek intellectual property protection. Second, because patents disclose chemical structures, we can apply advanced compu-

[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.

tational chemistry methods— specifically quantitative structure–activity relationship (QSAR) models—to predict multiple dimensions of compound hazard (e.g., Cherkasov et al., 2014), moving beyond coarse classifications of technologies as simply "dirty" or "clean" based on the presence or absence of specific substances. These methods allow us to predict a range of properties, including various forms of human health toxicity and environmental persistence, thereby providing a more accurate assessment of the direction of technical change and its associated societal multidimensional impacts.

To systematically link chemical compounds with patent documents, we rely on CAS SciFinder-n, 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 China National Intellectual Property Administration (CNIPA). 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 by their functional role within the patent—such as whether a given substance acts as a catalyst, excipient, or other active component of the chemical process—thereby providing detailed information on each compound's contribution to the patented invention. This classification allows us to exclude patents in which a chemical is mentioned but plays no active role in the formulation or reaction. Additionally, it assigns a unique CAS Registry Number (CAS Number) to each chemical compound to ensure the accurate and consistent identification of chemical compounds across international databases.

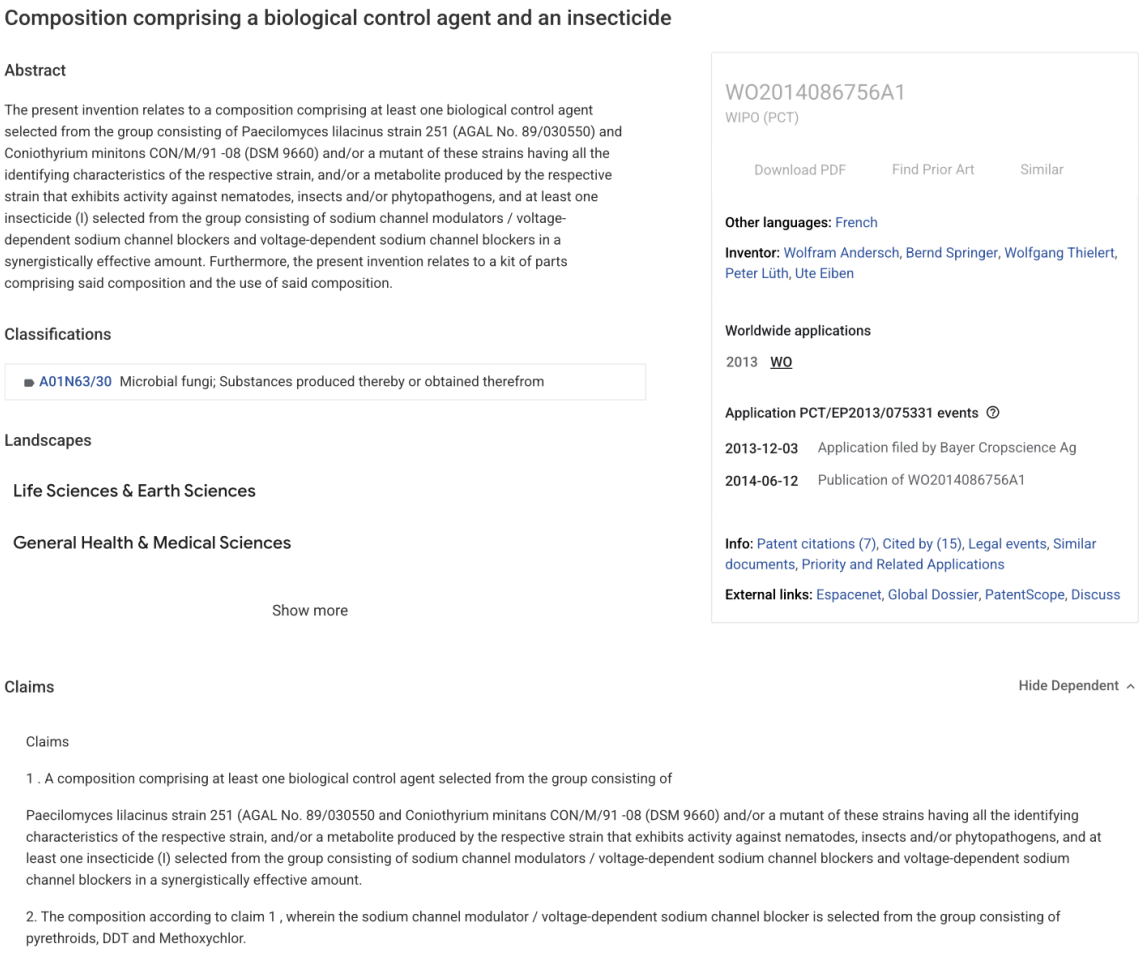
4.1.1 POP patents

Using the SciFinder-n 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-n is characterized by the following roles: "use", "use as a part of a mixture" or "use in preparation", etc.[2] To clarify further, selecting specific roles ensures that patents are excluded from the analysis if a POP is mentioned only as an

[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.

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-n 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 (one POP is excluded because there are no recorded patents using it).

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

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

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, an alternative to DDT is DDD (Dichloro-diphenyl-dichloro-ethane) —an organochlorine insecticide structurally similar to DDT but not subject to the 2004 SC ban (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 the 12 POPs (listed in Appendix Figure A1). 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. Our selection of ontology-based substitute patents covers 1,826,483 unique chemical compounds.

We now outline the approach adopted to differentiate regrettable patents from other 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 use the methodology proposed by Biggi et al. (2022), which in essence employs mathematical models to predict chemical properties based on molecular structure and accumulated evidence on compound behavior drawn from existing property data (Cherkasov et al., 2014; Zimmerman et al., 2020). Our analysis draws on computational toxicology, a branch of computational chemistry focused on assessing toxicological impacts, and in particular on quantitative structure–activity relationship (QSAR) models, which relate molecular structure

to toxicity and environmental hazard outcomes (Benfenati et al., 2013; Van Noorden, 2018).

To systematically classify patents as containing regrettable substitutes, we analyze all chemical compounds that SciFinder-n 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, (i) it is persistent and (ii) highly toxic for human beings and/or the environment.

To measure persistence (i), we focus on Persistent and Bioaccumulative (PB) endpoints derived from predicted toxicity. PB toxicity is evaluated using eight QSAR models, including IRFMN (covering soil, sediments, and water), KNN, Meylan, and the Mond-Gobas model (see Appendix Figure A2).

Next, to classify patents as highly toxic (ii), we adopt a conservative criterion based on the EU REACH regulation for identifying so-called "Substances of very high concern," an approach aligned with the United Nations Global Harmonized System of Classification and Labelling of Chemicals (GHS), which designates chemicals as highly toxic when they exhibit Carcinogenic, Mutagenic, or Reprotoxic (CMR) properties. In addition, following consultations with experts, we incorporate three environmental toxicity (ET) endpoints capturing harm at three trophic levels—algae, invertebrates, and fish—reflecting the central role of aquatic toxicity in environmental hazard and risk assessment. 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 A2). ET toxicity is determined through seven QSAR models targeting fish, daphnia magna, and algae, with classifications based on toxicity concentration thresholds (see Appendix Table A2).

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

[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.

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: (i) PB *and* (ii) CMR, PB *and* ET, or (i) PB, (ii) 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 alternatives. Using computational toxicology, we are also able to characterize the chemical features of all patents within the set of ontology-based substitutes. Among the alternative patents that do not fall under our definition of "regrettable," we were interested in constructing a comparison group comprising patents whose formulations contain no chemical compounds classified as PB, CMR, or ET—that is, patents lacking any individual POP-like characteristics. We refer to these as "safer" patents. We could identify 47,701 safer patents, corresponding to 11,624 patent families. We must note that the absence of PB, CMR, or ET classifications does not imply that these patents are entirely benign, as they may still involve chemicals associated with other, less severe forms of toxicity (e.g., endocrine disruption or liver toxicity). As discussed above, our classification deliberately targets only the most hazardous toxicity profiles and is therefore intentionally conservative.

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 and

safer patents (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

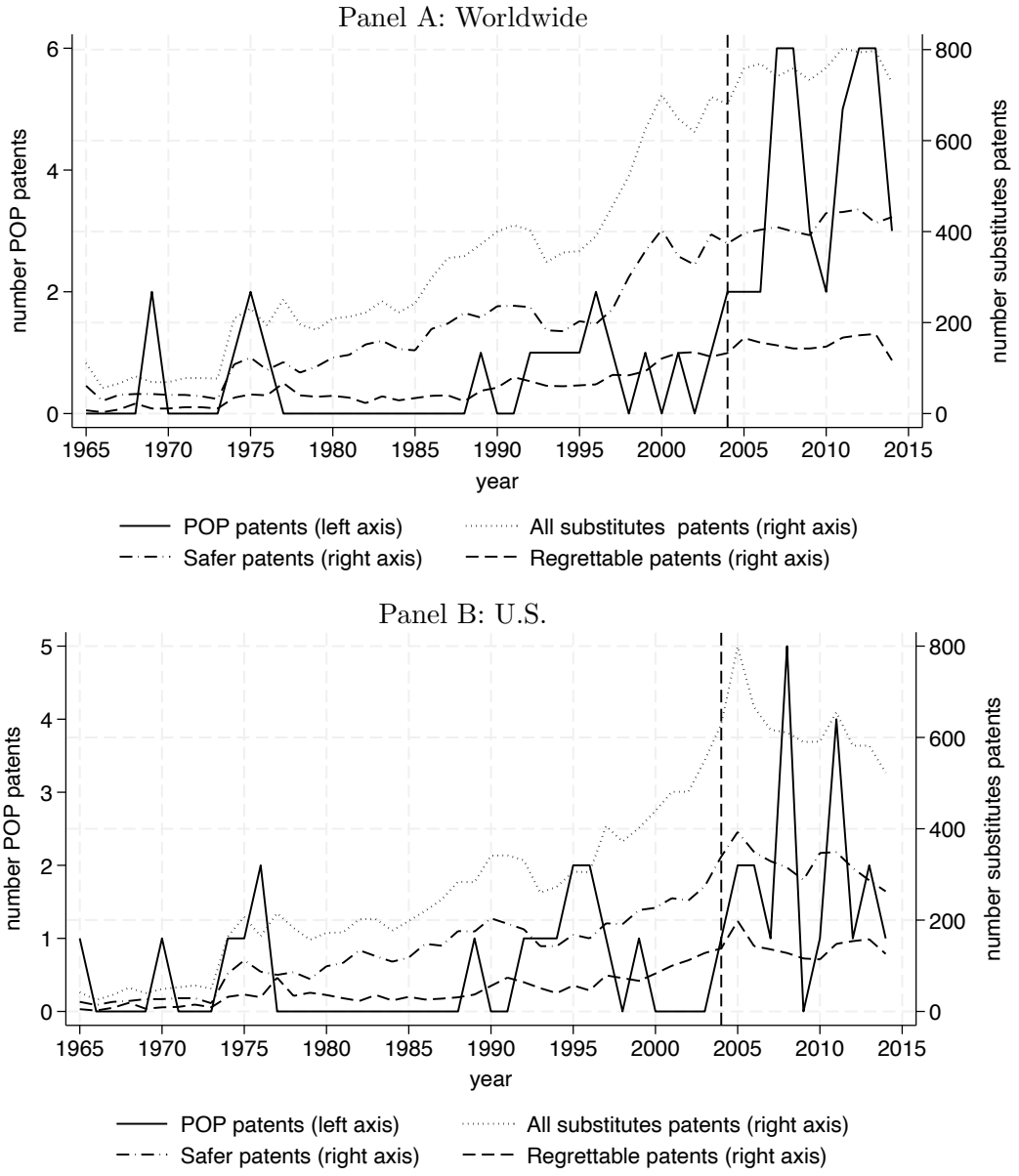
Note: The table reports the composition of the dataset used in the analysis at the patent application-level and DOCDB family-level. The data cover the patenting activity of 11 POPs and their ontology-based chemical substitutes in 89 patent offices worldwide over the period 1965-2014. Note that a patent 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 USPTO, followed by EPO, and by the patent offices of Japan, China, Germany, Canada, South Korea, Australia and Taiwan (see Appendix Figure A3). 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 A7).

Figure 2 (panel A) reports the number of patent families filed worldwide over time, distinguishing between patents related to the 12 POPs (left axis), the full set of ontology-based substitute patent families, and the subgroups of regrettable and safer patent families (right axis). Figure 2 (panel B) presents the corresponding trends for the United States. In both settings, we observe an overall increase in patenting activity across all categories, including patents related to the 12 POPs. The latter remain very limited in number and likely reflect

[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.

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) entered into force, leading to the banning of POPs. To avoid double-counting of patent twins, only the first filing within each patent family is considered.

residual demand for POP chemicals in jurisdictions where regulation is weak or uneven (Biggi et al., 2024), particularly in parts of Asia (Van den Berg, 2009).

While both regrettable and safer patent families display upward trends over time, our primary empirical objective is to identify the impact of the Convention on the growth of regrettable patents specifically. As mentioned, safer patents are included only for comparative purposes. The reason for this is that the existence of safer alternatives does not, in itself, prevent firms from developing, patenting, and commercialising hazardous substances. Even a single regrettable innovation that reaches the market may generate substantial harm to human health and the environment, irrespective of the simultaneous availability of safer options. In other terms, understanding the drivers of regrettable patenting—independently of trends in safer alternatives—is essential for assessing whether international regulation effectively discourages the development of hazardous chemical innovations.

Figure 3 plots the average share of harmful compounds in regrettable patents filed worldwide over time. Panel A shows that the combined share of PB, CMR, and ET compounds declines beginning in the 1980s. By contrast, Panels B and C indicate that the share of PB *and* CMR compounds and the share of PB *and* ET compounds increase starting around the entry into force of the Stockholm Convention.

Table 3 reports the top 15 patent applicants in our dataset, ranked by patent portfolio size, defined as the total number of POP-related, regrettable, and safer patent families filed worldwide between 1965 and 2014. Notably, major chemical companies appear to be active across both categories, engaging in the development of both regrettable and safer chemical innovations.

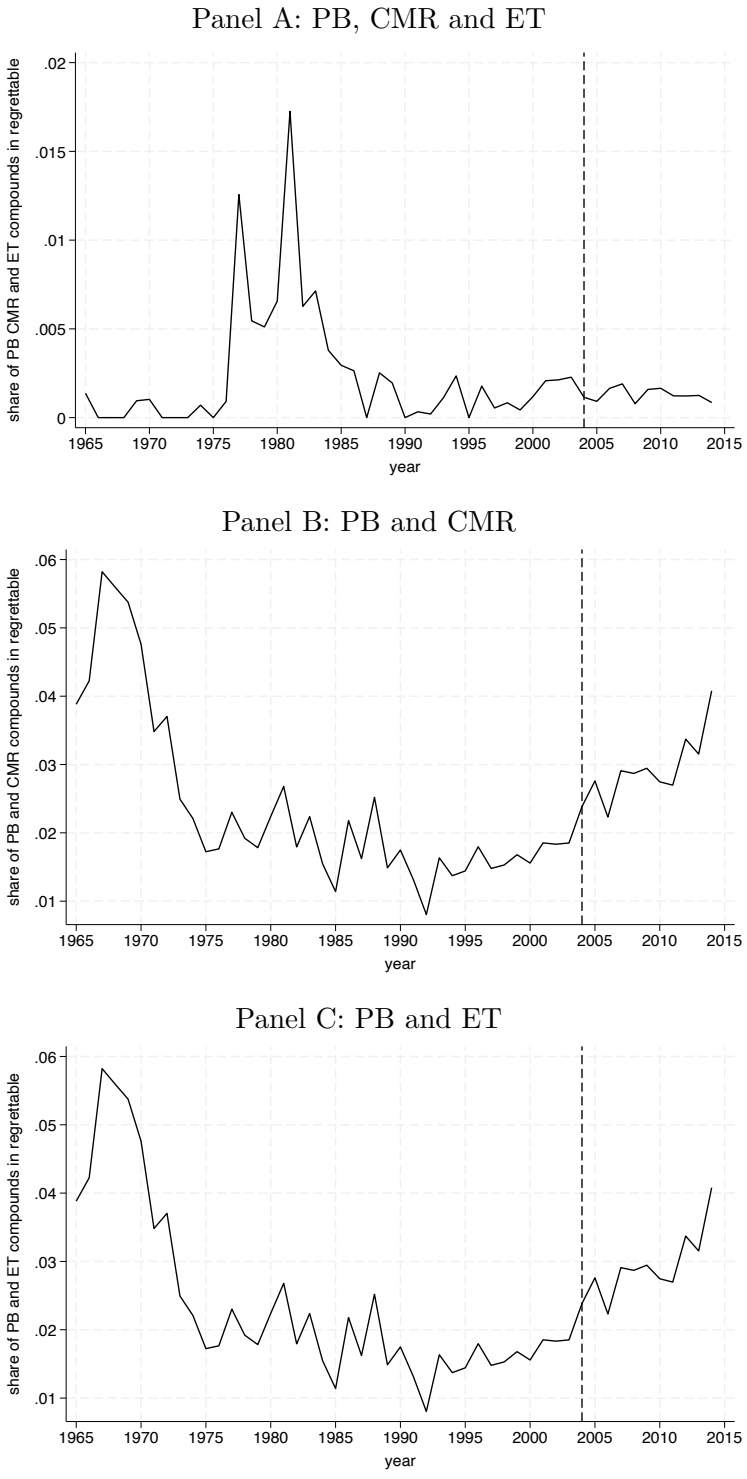
4.3 Empirical strategy

We examine the impact of a chemical treaty on the development of alternative technologies (Dugoua, 2025), focusing specifically on those classified as regrettable using computational toxicology. A central challenge in this setting is the construction of a credible control group—one that remains unaffected by the Convention—since any spillovers from treated to control units would violate a core identifying assumption of the difference-in-differences (DID) framework.

To address this, we construct a control group using chemical ontology, comprising "safer" patents that are structurally and functionally similar to the treatment group but originate from entirely distinct technological domains.[5] This distinction is crucial. By drawing patents from

[5]To ensure genuine separation, we exclude all safe alternatives assigned to any full-digit International Patent

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 year the SC entered into force (2004). To avoid double counting of patent twins, only the first filing within each patent family is considered.

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.

unrelated technological domains, we ensure that the corresponding chemicals were developed for purposes other than replacing the targeted POPs. As a result, these chemicals are unlikely to serve as substitutes for the regulated substances, 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 the type of POP and t is the year of the filing of the DOCDB patent application. The dummy

Classification (IPC) class containing at least 10 regrettable patents.

$REGRETTABLE_{k,c,p,t}$ equals 1 for regrettable patents (i.e., patents that have at least one CMR and PB; or ET and PB, or one CMR, ET and PB compound in the chemical formulation), 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. 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 both worldwide and in the U.S., which is not observable for the control group. To assess the plausibility of the parallel trend 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:

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

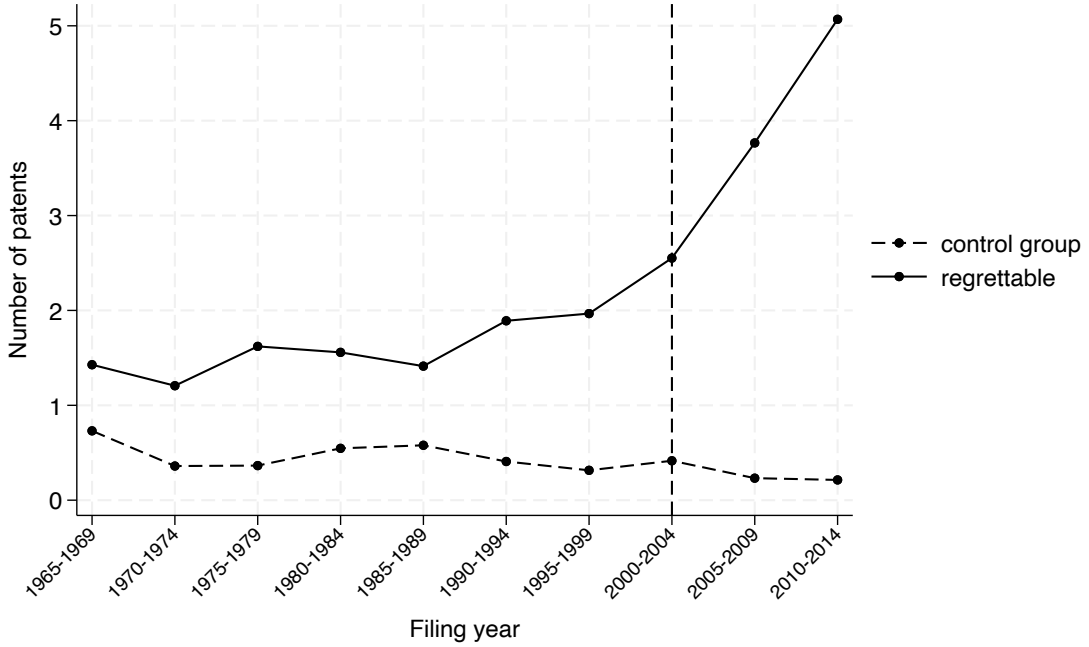
In this equation, the year 1965 serves as the baseline omitted period. Figure 5 illustrates the estimated coefficients along with their 95% confidence intervals. The results confirm that the increase in regrettable patents did not begin before 2004, with the effect becoming especially pronounced after 2005.[6] This finding supports the parallel trend assumption, indicating that any observed differences post-2004 are likely attributable to the SC.

Table 4 presents our main DID regression results. Column 1 includes patent office fixed

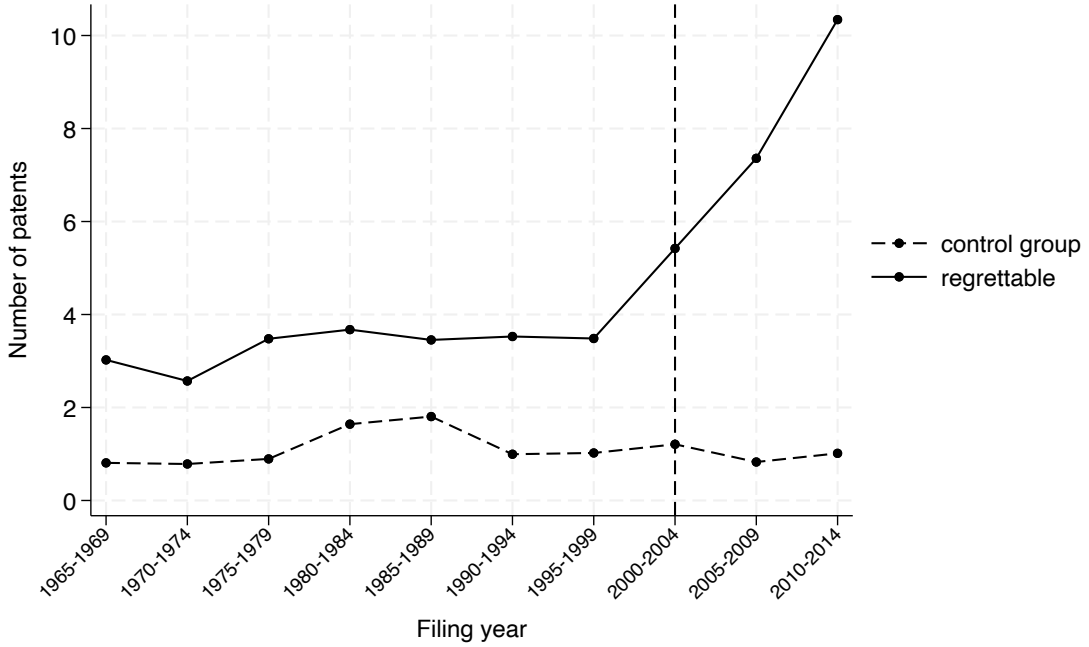
[6]The parallel trend assumption holds also when considering U.S., EPO or CNIPA patents only (see Appendix, Figure A2, A3, A4).

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

Panel A: Worldwide

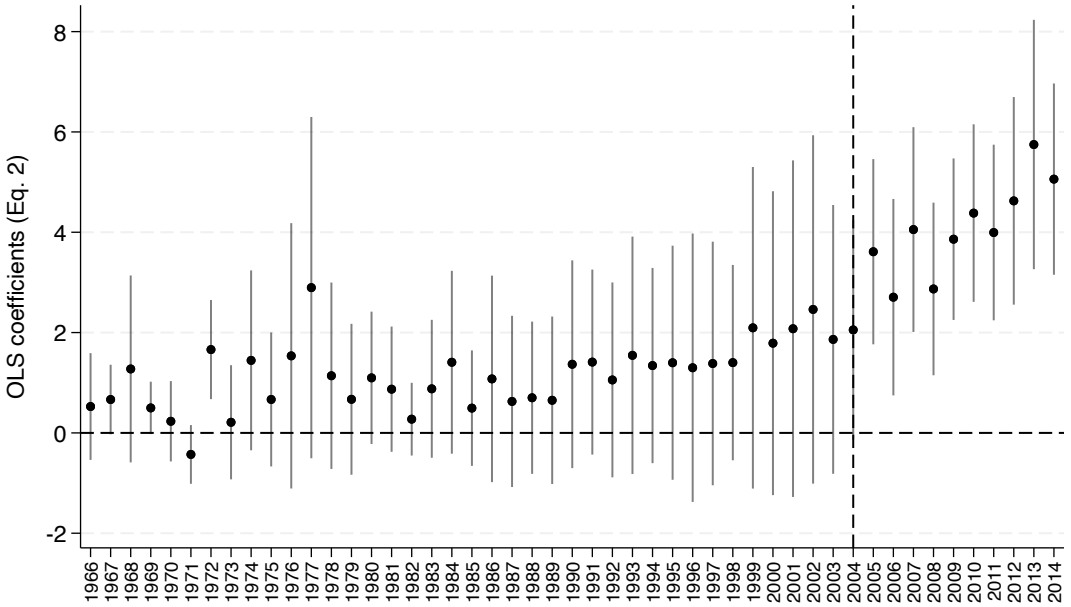


Panel B: U.S.



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.

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.

Table 4: Difference-in-difference main results

	Worldwide			U.S.	EP	CN
POST	0.0333	0.137	0.496	1.847	1.529	2.289
	(0.124)	(0.114)	(0.418)	(1.409)	(1.195)	(1.783)
REGRETTABLE	1.408***	1.408***	1.408***	2.513*	2.594*	1.829**
	(0.490)	(0.490)	(0.490)	(1.266)	(1.480)	(0.903)
POST × *REGRETTABLE*	2.743***	2.743***	2.743***	4.959***	4.425***	4.326***
	(0.540)	(0.540)	(0.540)	(1.227)	(1.184)	(1.001)
Observations	110,484	110,484	110,484	8,714	6,660	5,110
R-squared	0.098	0.106	0.191	0.337	0.340	0.295
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

effects, Column 2 adds POP-type fixed effects, and Column 3 further incorporates CAS Number fixed effects. Columns 4, 5 and 6 restrict the sample to patents filed at the USPTO, EPO and CNIPA. 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 between 4.42 and 4.95 in individual patent offices, compared to the control group. When adjusted for the pre-2004 yearly averages of regrettable patent families, these figures imply a 150% rise in regrettable patent families worldwide, a 135% rise in the U.S., a 141% rise at EPO and a 215% rise at CNIPA.[7]

A natural question at this point is whether the SC may have simultaneously encouraged the development of safer alternatives, rather than only affecting regrettable patents. This question is particularly relevant given the upward trend in safer patents documented earlier, which raises the possibility that innovation could have shifted toward these less hazardous chemicals too. To address this, Figure 6 presents the estimated coefficients and their 95% confidence intervals from an alternative specification of Equation (2), in which the treated group is defined as the safer substitutes rather than the regrettable ones. The results indicate no significant impact of the SC on the development of safer substitutes. Taken together, Figures 5 and 6 suggest that, rather than steering innovation toward safer alternatives, the SC may have incentivized the creation of regrettable chemical inventions.

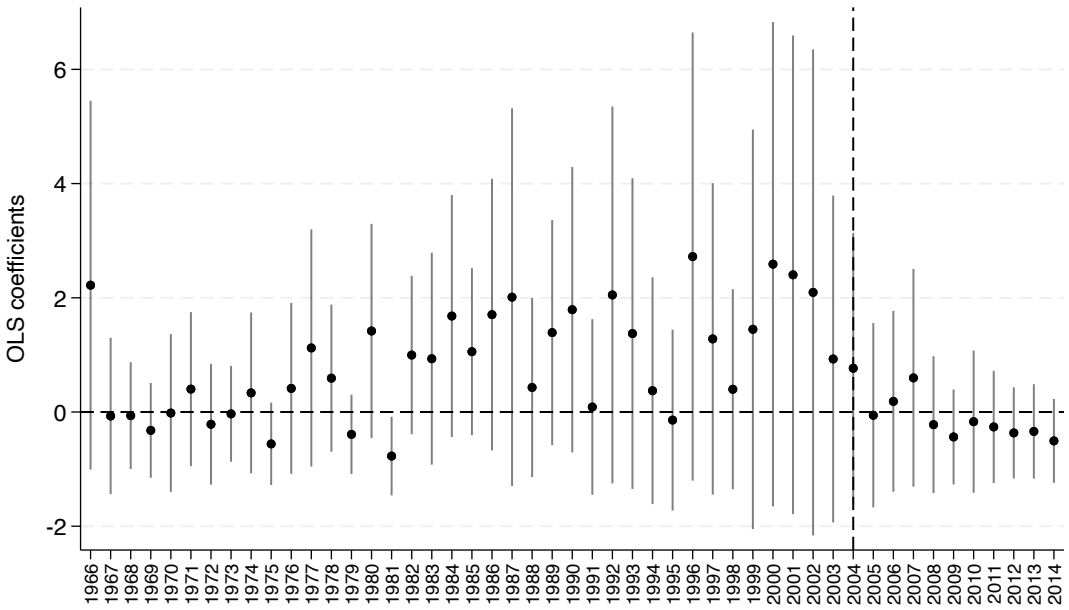
5.2 Heterogeneity across POP types

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.[8] However, when we normalize the coefficients by the average number of regrettable patent families filed prior to 2004 for 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

[7] The pre-2004 yearly average of regrettable patent families is 1.83 globally, 3.67 in the U.S., 3.13 at EPO and 2.01 at CNIPA.

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

Figure 6: Impact of the Stockholm Convention on safer patent families worldwide



Notes: OLS coefficient estimates of Equation (2) with 95% confidence intervals are reported. In this specification, the treated group is defined as the SAFER substitutes rather than REGRETTABLE, as in the main analysis. The dependent variable is the number of patent family applications filed worldwide. The data cover the period 1965-2014.

stem from the fact that certain POPs, such as PCB, 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 A5 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 and PCB, for the reasons mentioned above). DDT represents a unique case, as shown in Figure A6, 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 and Table 7.

First, to address the observed heterogeneity across POPs and minimize potential bias in

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

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

	1	2	3	4	5	6
	Excluding DDT	Shorter pre-treatment period	Excluding 2001-2004	Early vs. late ratification	Negative Binomial	Regrettable above-the-median
POST	0.513	0.211	0.504	0.299	-0.273*	0.142
	(0.430)	(0.419)	(0.428)	(0.374)	(0.142)	(0.203)
REGRETTABLE	1.418***	1.740**	1.298***	1.399***	1.783***	0.649***
	(0.510)	(0.744)	(0.420)	(0.513)	(0.369)	(0.080)
POST × *REGRETTABLE*	2.863***	2.412***	2.853***	2.711***	1.776***	2.975***
	(0.565)	(0.685)	(0.519)	(0.625)	(0.221)	(0.551)
LATE RATIFICATION				0.111		
				(0.372)		
POST × *LATE RATIFICATION*				0.309**		
				(0.142)		
REGRETTABLE × *LATE RATIFICATION*				-0.129		
				(0.165)		
POST × *REGRETTABLE* × *LATE RATIFICATION*				0.0660		
Observations	105,538	88,378	104,410	99,246	110,484	110,484
Patent office FE	✓	✓	✓	✓	✓	✓
Pop-type FE	✓	✓	✓	✓	✓	✓
CAS Number FE	✓	✓	✓	✓	✓	✓

OLS estimates in Columns 1, 2, 3, 4 and 6. Negative Binomial estimates in Column 5. Alternative definition of REGRETTABLE applied in Column 6. All patent offices included. Regional patent offices (e.g., EPO) are excluded in Column 4. Robust s.e. in parentheses, clustered by CAS Number.
Legend: *** p<0.01, ** p<0.05, * p<0.1

our estimates, we re-estimate Equation (1) by excluding DDT (Column 1). The results remain consistent with the main estimations (Table 4), indicating a 154% increase in regrettable patents worldwide.

Second, we re-estimated the analysis using a reduced pre-treatment period. Specifically, we restricted the sample to a shorter time window prior to the shock (1990-2014) in order to verify that the estimated treatment effects are not driven by long-term pre-existing trends. The results (Column 2, Table 6) obtained under this restricted specification confirm the baseline estimates.

Third, in our main analysis we define the pre- and post-treaty periods with reference to the year in which the SC entered into force (2004), rather than the year of its signature (2001). To account for potential anticipation effects, we exclude the intervening years between 2001 and 2004 in Column 3 of Table 6; the results remain robust. In Column 4, we further examine whether the effect of the SC varies according to the timing of ratification, distinguishing between countries that ratified promptly in 2004 and those that did so at a later date. While the majority of countries ratified in 2004, a subset delayed ratification by several years.[9] In these countries, the SC may not have created sufficient incentives for innovation in alternative chemicals until its formal ratification. To test this hypothesis, we interact our main coefficient of interest with a dummy variable ($LATE\ RATIFICATION$) equal to 1 if the SC was ratified in 2004 and 0 if the ratification occurred later. The results show that the timing of ratification does not significantly influence the impact of the SC.[10]

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 5). We also 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 of the invention. 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

[9]Detailed information on the ratification dates of the SC by country is available at https://chm.pops.int/countries/statusofratifications.

[10]In this regression analysis, we restrict our sample because regional patent offices are excluded.

(Table 6, Column 6) remain consistent.

Finally, we perform a placebo test by artificially shifting the treatment date one year, two years and nine years earlier and restricting the sample to the pre-treatment period. As shown in Table 7, the placebo interaction is always statistically insignificant, consistent with the absence of anticipatory effects. This is further supported by the event-study plot showing no pre-treatment trends.

Table 7: Difference-in-difference results - Placebo test

	Worldwide			U.S.		
	post 1995	post 2001	post 2003	post 1995	post 2001	post 2003
POST	0.330	0.246	0.339	0.902	1.110	1.205
	(0.200)	(0.184)	(0.242)	(0.653)	(0.974)	(1.025)
REGRETTABLE	1.122***	1.299***	1.375***	2.221**	2.344**	2.458**
	(0.281)	(0.421)	(0.474)	(0.905)	(1.119)	(1.216)
$POST \times REGRETTABLE$	0.725	0.898	0.608	0.898	1.557	1.281
	(0.580)	(0.650)	(0.403)	(1.219)	(1.532)	(1.441)
Observations	49,950	49,950	49,950	4,818	4,818	4,818
R-squared	0.158	0.156	0.154	0.374	0.373	0.371
Patent office FE	✓	✓	✓	✓	✓	✓
Pop-type FE	✓	✓	✓	✓	✓	✓
Compound FE	✓	✓	✓	✓	✓	✓

OLS estimates of Equation 1. Treatment year shifted one, two and nine years earlier than 2004.
Robust standard errors in parentheses, clustered by CAS Number.
Legend: *** p<0.01, ** p<0.05, * p<0.1

6 Mechanisms

In this section, we explore the mechanisms that may underlie our main findings, assessing plausible explanations for the observed effects. We classify these mechanisms into three broad categories: (i) Technological path dependency, capturing cumulative constraints on innovation, (ii) Scientific uncertainty, reflecting the limited scientific knowledge about the hazards of the alternative chemical formulations, and (iii) Country-level economic and institutional contexts, encompassing country-level factors that may encourage or discourage the use of regrettable chemicals.

Technological path dependency. Embedded expertise in producing POP-like chemicals may constrain technological directionalities, reducing incentives to develop safer alternatives. If this mechanism is at work, regrettable substitutes should more closely resemble POPs than safer alternatives if they are too distant. To assess this, we measure molecular similarity between substitute patents and POPs using Tanimoto scores (Krieger et al., 2022), which quantify

overlap in chemical substructures and proxy potential functional similarity. Comparing regrettable and safer patents, Table 8 reports results from a patent-level regression of the Tanimoto score on a $REGRETTABLE$ indicator, controlling for the number of compounds and including POP-type, patent office, year, IPC class, and applicant fixed effects (Column 5 shows the main specification). The results indicate that regrettable patents are significantly more similar to POPs than safer patents, consistent with a technological path dependency effect.

Table 8: Chemical similarity (Tanimoto Score) between substitutes and POP patents

	1	2	3	4	5
REGRETTABLE	0.00653***	0.00769***	0.00703***	0.00430***	0.00262*
	(0.001)	(0.001)	(0.001)	(0.001)	(0.001)
NUMBER OF COMPOUNDS		-2.83e-05***	-3.44e-05***	-5.10e-05***	-3.94e-05***
		(0.000)	(0.000)	(0.000)	(0.000)
Observations	384,652	384,652	384,652	384,652	384,652
R-squared	0.486	0.486	0.490	0.497	0.539
Pop-type FE	✓	✓	✓	✓	✓
Year FE	✗	✗	✓	✓	✓
Patent Office FE	✗	✗	✓	✓	✓
IPC class FE	✗	✗	✗	✓	✓
Applicant FE	✗	✗	✗	✗	✓

OLS estimates. Robust standard errors in parentheses, clustered at the applicant level.
Legend: *** p<0.01, ** p<0.05, * p<0.1

We further test whether prior knowledge amplifies this effect by interacting the SC treatment with the cumulative stock of POP patents in each patent office up to 2004.[11] Table 9, column 1, shows that regrettable substitutes post-SC are more frequent in offices with a larger pre-2004 POP patent stock, providing additional evidence that path dependency shapes the rise in regrettable innovation.

Scientific uncertainty. Another plausible interpretation of our results is that firms (inventors) may have lacked sufficient scientific knowledge to characterize, at the time of the invention, a chemical compound as "regrettable". To examine this, we draw on toxicological evidence, based on the scientific literature reporting health and environmental hazards of the regrettable chemicals in our patents. Using CAS Numbers for regrettable substitutes (as identified in Section 4.1.2), we retrieved 4,022 peer-reviewed studies published between 1965 and 2014 from the Scopus database, focusing on the subject area "Toxicological studies." These publications document key toxicity endpoints—including carcinogenicity, mutagenicity, and persistence—providing a comprehensive record of hazardous properties for these compounds. By

[11]The stock is calculated with a 15% depreciation rate: $KPAT_t = PAT_t + (1-\delta)KPAT_{t-1}$.

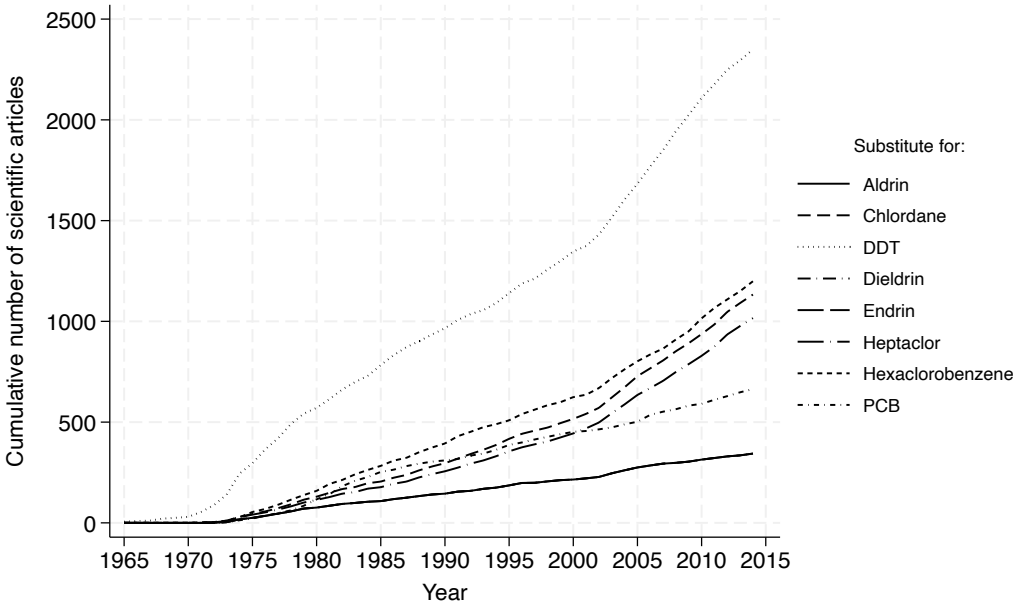
Table 9: Difference-in-difference results - Mechanisms

	1	2	3	4	5
	Stock of POPs patents	Toxicological scientific articles	% Agri Land	GDP	Environmental Policy Stringency
POST	0.513	0.618	-0.495***	0.681	1.182**
	(0.701)	(0.548)	(0.108)	(0.449)	(0.585)
REGRETTABLE	0.922***	1.444**	1.389**	1.434***	1.576***
	(0.197)	(0.669)	(0.555)	(0.359)	(0.519)
POST × REGRETTABLE	2.244***	2.696***	2.052***	2.067***	3.787***
	(0.360)	(0.801)	(0.557)	(0.584)	(1.011)
COUNTRY MEASURE	0.516		-1.188***	2.043**	-2.735
	(0.378)		(0.263)	(0.820)	(1.642)
POST × COUNTRY MEASURE	-0.134		0.248**	-0.0909**	-0.482***
	(0.192)		(0.117)	(0.042)	(0.155)
REGRETTABLE × COUNTRY MEASURE	0.419		-0.00213	-0.00164	-0.0567*
	(0.306)		(0.027)	(0.016)	(0.031)
POST × REGRETTABLE × COUNTRY MEASURE	0.693**		0.189***	0.0521**	-0.566**
	(0.266)		(0.054)	(0.023)	(0.241)
POST × LOG TOXIC. ARTICLES		-0.0524			
		(0.078)			
REGRET × LOG TOXIC. ARTICLES		-0.0158			
		(0.086)			
POST × REGRET × LOG TOXIC. ARTICLES		0.0208			
		(0.242)			
Observations	110,484	110,484	94,412	92,812	64,960
R-squared	0.179	0.191	0.191	0.195	0.190
Patent Office FE	✓	✓	✓	✓	✓
Pop-type FE	✓	✓	✓	✓	✓
CAS Number FE	✓	✓	✓	✓	✓

OLS estimates. Robust standard errors in parentheses, clustered by CAS Number.
The variable COUNTRY MEASURE is:
1) Stock of POPs patents, computed with a depreciation rate of 15% (column 1).
2) % of agricultural land included in log terms, based on data from FAOSTAT (column 3).
3) GDP per capita included in log terms, based on data from World Bank Open Data (column 4).
4) Environmental Policy Stringency (EPS) index (Botta and Koźluk, 2014), available for OECD countries only (column 5).
The variable toxicological articles is included in log terms and is based on data from Elsevier SCOPUS (column 2).
Regional patent offices (e.g., EPO) are excluded from the analysis in Column 3, 4 and 5.
Legend: *** p<0.01, ** p<0.05, * p<0.1.

grouping studies according to the POP each substitute was intended to replace, we reconstruct the historical availability of toxicological evidence. Figure 7 shows that evidence on the hazards of substitutes was already available well before the SC, with a substantial body of literature dating to 1975–1980. This indicates that firms had access to early warning signals from the scientific community. To formally test this mechanism, we augment our baseline model (1) with a triple interaction including the cumulative number of toxicological publications available before 2004 (logged). Table 9, column 2, shows that the filing of regrettable substitutes is unaffected by prior toxicological knowledge, questioning the idea that the post-SC increase in regrettable substitutes was driven by a complete ignorance on the toxicological hazards of these molecules. Incidentally, QSAR models for predicting chemical hazards, widely used by regulatory agencies such as the U.S. EPA since the early 1980s, further indicate that tools for hazard assessment were available prior to the SC.

Figure 7: Toxicological scientific literature on regrettable compounds



Note: The figure shows the cumulative number of scientific articles published between 1965 and 2014 that report toxicological evidence on substitute technologies for each POP. Data were retrieved from Elsevier Scopus. No scientific articles were found for PCDD/PCDF, Mirex, or Toxaphene.

Country-level economic and institutional context. Cross-country differences may also help explain the post-SC rise in regrettable patenting. Although the Convention establishes binding commitments to eliminate POPs, it grants countries substantial discretion in implementation, generating heterogeneity in enforcement, monitoring, and regulatory stringency.

We examine two country-level dimensions that may shape firms' responses to the SC. The

first captures economic incentives that may encourage regrettable substitution, proxied by the intensity of agricultural activity and the size of the economy. The second reflects environmental regulatory orientation, which may discourage the development of hazardous substitutes.

As concerns the first dimension, because many POPs have historically played a critical role in agriculture (Namiki et al., 2013), countries with more intensive agricultural activity may face stronger pressures to rapidly replace these substances. In such settings, the urgency to sustain agricultural output may favour the development of functionally similar—yet regrettable—substitutes. Consistent with this mechanism, we find that the effect of the SC on regrettable patenting is significantly stronger in countries with a higher share of agricultural land (Table 9, column 3).

We further find that regrettable patenting increases more sharply in countries with higher GDP per capita (Table 9, column 4), indicating that wealthier countries have been more active in technological responses to the SC—though not necessarily in safer directions. Together, these results suggest that national economic structures and incentives condition how international environmental regulation shapes the direction of innovation.

To capture differences in regulatory orientation, we rely on the Environmental Policy Stringency (EPS) index (Botta and Koźluk, 2014), a composite measure of the stringency and enforcement of environmental regulation across different policy domains. We incorporate a triple interaction between the SC treatment and the continuous EPS measure into our baseline specification. The results show that the incentive to patent regrettable substitutes following the SC is significantly stronger in countries with lower EPS (Table 9, column 5).[12]

Taken together, these findings suggest that national economic structures and environmental orientation may at least partially explain the effect of the SC on the rise of regrettable patents.

7 Conclusion

This paper contributes to the literature on directed technical change by examining not only whether firms develop substitute technologies in response to regulation, but also the quality of those substitutes. Much of the existing literature implicitly treats alternatives as "clean" once a targeted ingredient is removed. In this view, regulation and market incentives successfully redirect innovation toward socially desirable outcomes (Aghion et al., 2016; Calel and Deche-

[12]We note that the EPS index is available only for OECD countries; accordingly, the sample is restricted to OECD members, and regional patent offices (e.g., the EPO) are excluded.

zleprêtre, 2016; Veugelers, 2012; Dugoua, 2025). This assumption, however, presumes that substitutes are genuinely safer—a premise that need not hold.

Drawing on insights from the chemistry literature on "regrettable substitutions" (Zimmerman and Anastas, 2015), we challenge this assumption. Focusing on substitutes for 12 persistent organic pollutants (POPs) banned under the Stockholm Convention (SC), we combine patent data with computational toxicology to classify alternative technologies as regrettable or safer. While consistent with prior work we find that the SC stimulated substitute innovation, our results show that this response was driven by regrettable substitutes—chemicals that are not banned but exhibit POP-like toxicity and persistence. DID estimates indicate that regrettable patents increased significantly more than safer ones after the SC, suggesting that regulation redirected innovation without substantially improving its environmental quality.

We further investigate the mechanisms underlying this pattern. First, we find support to the role played by technological path dependency in shaping the direction of technical change, as regrettable substitutes are chemically closer to POPs than safer alternatives. Second, we rule out a scientific ignorance explanation: extensive toxicological evidence documenting the hazards of these substitutes existed well before the SC, and variation in prior scientific knowledge does not moderate the regulatory effect. Finally, we show that country-level incentives and institutions matter. The increase in regrettable innovation is stronger in countries with greater agricultural intensity, higher income levels, and weaker environmental policy stringency, highlighting how domestic economic structures and regulatory environments may provide some cues to explain our findings.

Our results carry several implications. Conceptually, they underscore the importance of analysing the direction of innovation by overcoming binary "clean versus dirty" classifications and adopting more granular, multidimensional measures of technological harm. From a policy perspective, our findings caution against relying on such unidirectional approaches to study the effects of regulations on harmful technologies. When regulation narrowly targets specific substances, firms may respond with privately optimal but socially suboptimal innovations. Effective policy must therefore shape not only the rate but also the direction of technological change, incorporating forward-looking assessments of hazards and promoting genuinely safer alternatives before harmful trajectories become entrenched.

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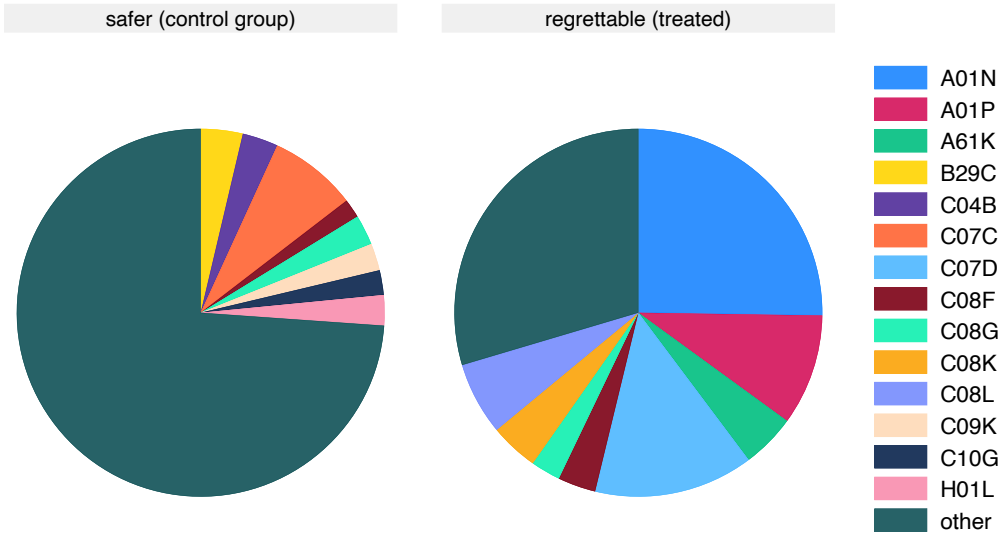
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Online apppendix

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.

Table A1: 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

Table A2: Toxicity predictions. Criteria for classification

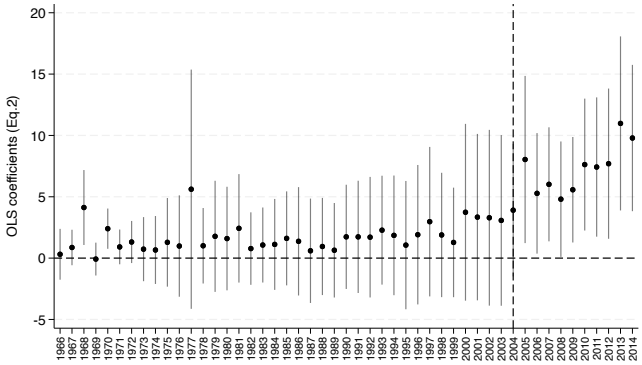
Toxicity class	**Toxicity endpoint**	**QSAR models**	**Scale of possible results**	**Criteria for classification**
PB (Persistent or Bioaccumulative)	Persistence	IRFMN (Soil, Sediments, Water)	nP (not persistent); P (persistent); vP (very persistent)	Prediction = 'P', 'vP' + Good reliability (in one 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 (CAESAR, ISS, SARpy, KNN)	Carcinogen; NON-Carcinogen	Prediction = 'Carcinogen' + Good reliability (in one or more QSAR)
	Mutagenicity		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)

Table A3: Frequency of patent files by the different patent offices

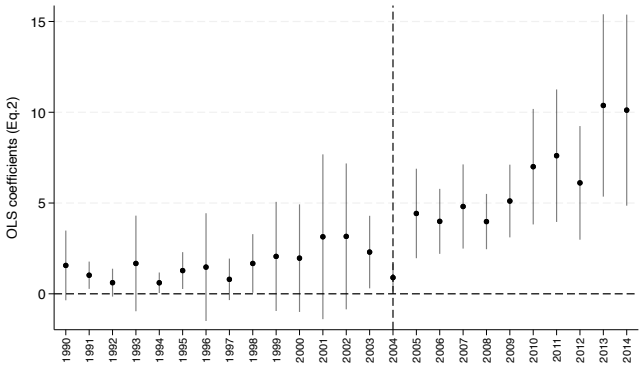
Patent Office	Freq.	Percent	Cum.
US	15,820	19.62	19.62
EP	9,656	11.97	31.59
JP	7,585	9.41	41
CN	6,111	7.58	48.58
DE	5,606	6.95	55.53
CA	4,647	5.76	61.29
KR	4,444	5.51	66.8
AU	2,905	3.6	70.4
TW	2,805	3.48	73.88
BR	2,702	3.35	77.23
ES	2,318	2.87	80.1
AT	1,986	2.46	82.56
MX	1,373	1.7	84.26
GB	1,269	1.57	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 A2: Impact of the Stockholm Convention on regrettable patents in the U.S.



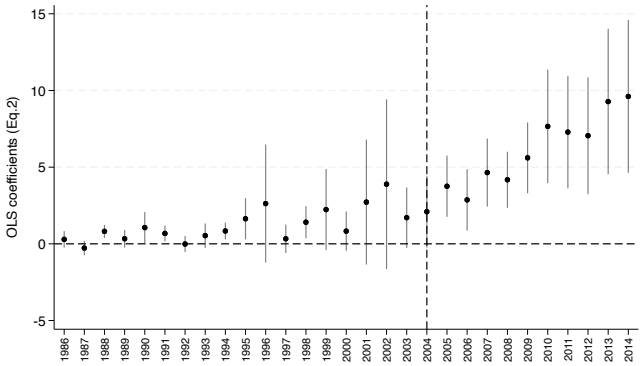
Notes: OLS coefficient estimates of Equation 2 (and their 95% confidence intervals) are reported. The dependent variable is the number of patent applications filed in the U.S. in the period 1966-2014.

Figure A3: Impact of the Stockholm Convention on regrettable patents at EPO



Notes: OLS coefficient estimates of Equation 2 (and their 95% confidence intervals) are reported. The dependent variable is the number of patent applications filed at EPO in the period 1990-2014.

Figure A4: Impact of the Stockholm Convention on regrettable patents at CNIPA



Notes: OLS coefficient estimates of Equation 2 (and their 95% confidence intervals) are reported. The dependent variable is the number of patent applications filed at CNIPA in the period 1986-2014.

Figure A5: Impact of the Stockholm Convention on regrettable patent families across POPs

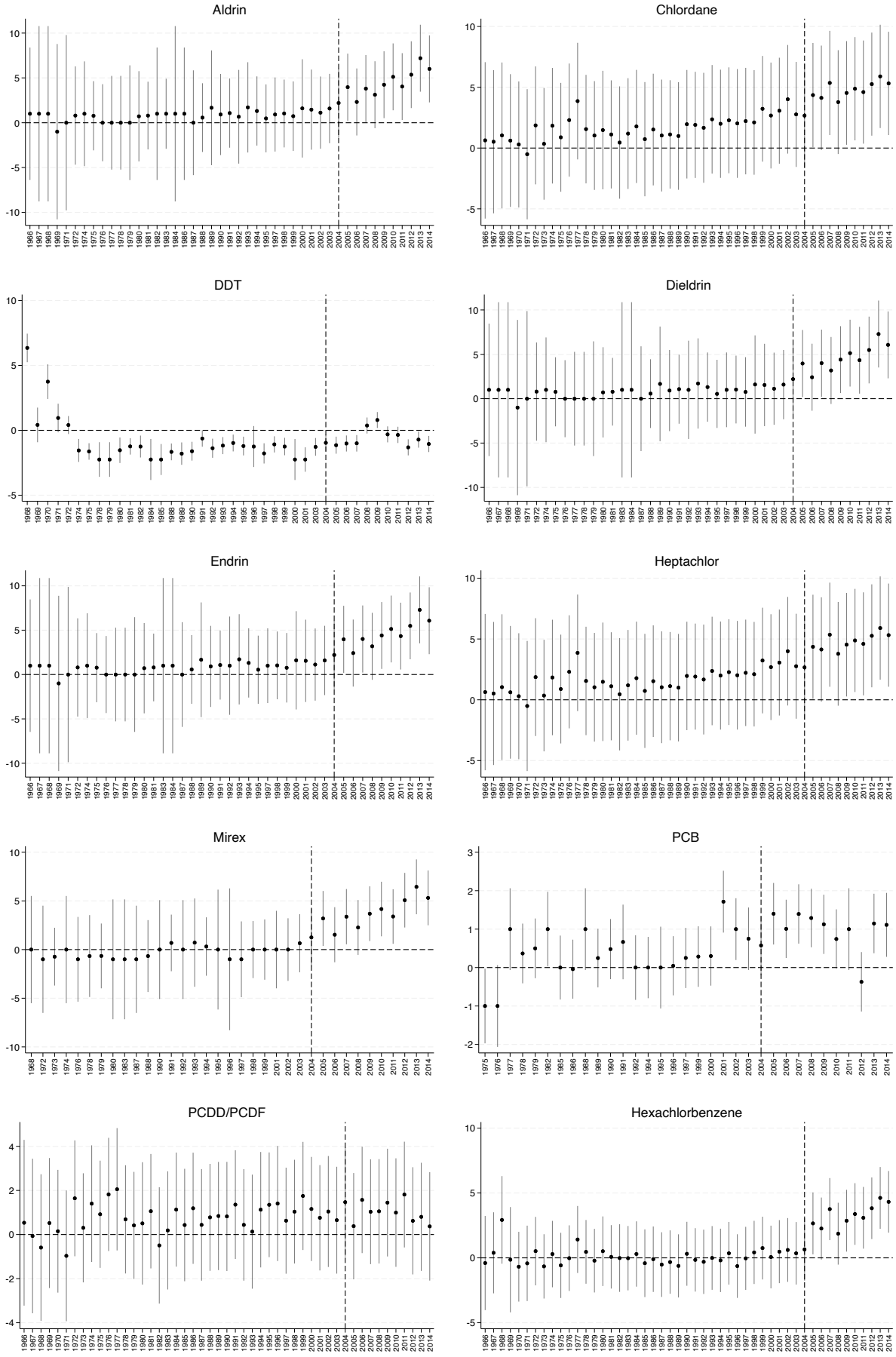


Figure A6: Impact of the Stockholm Convention on DDT patent families - the U.S. case

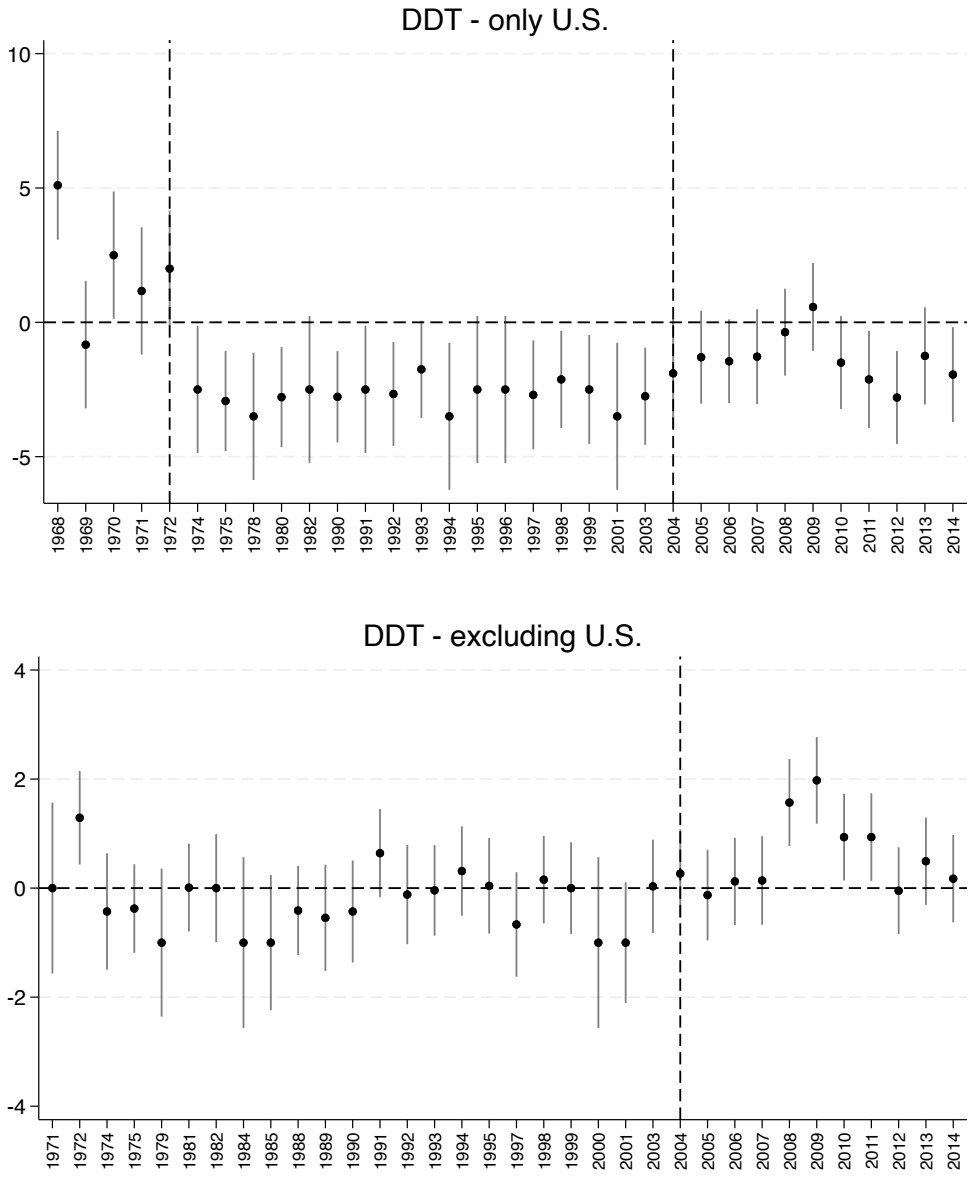
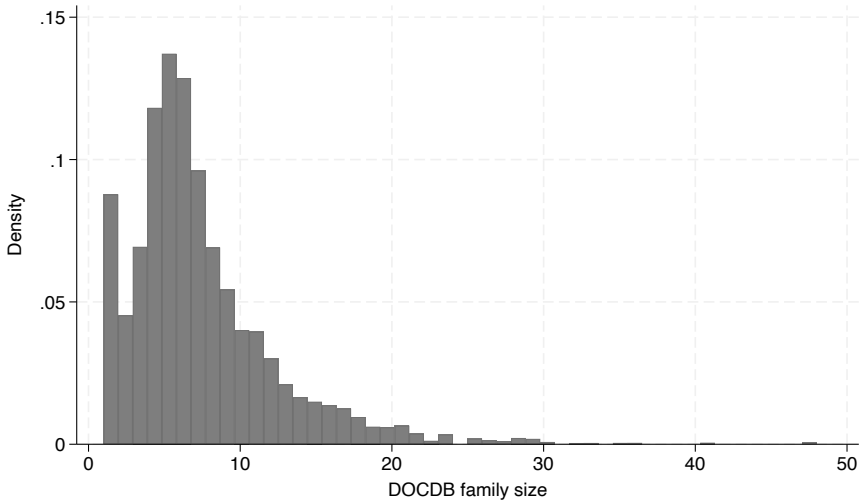


Figure A7: Distribution of patent family size



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