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Patent Toxicity

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Abstract
A toxic-free world is one of the goals of the European Green Deal and a key objective of the World Health Organization Inter-Organization Programme for the Sound Management of Chemicals. However, although use of some toxic chemicals is being banned, others continue to be developed. We consider this motivation for a closer examination of the toxicity of chemical inventions. We combine patent analysis with computational toxicology and develop a methodological roadmap to measure patent toxicity, that is, the extent to which a patent includes "components" (or compounds) that are toxic to humans and/or the environment. To illustrate our proposed methodology, we analyse the toxicity of ten well-known hazardous chemicals. The measurement of patent toxicity opens up interesting avenues for future research and, potentially, has some strong policy implications.

Keywords: Patents; computational toxicology, chemical inventions.

JEL Codes: O3; L65.

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1. Introduction

We are familiar with using patents to measure innovative output (Griliches, 1990) and to account for the characteristics of different inventions. Scholars measure quality and value using patent citations (Hall and Martin, 2005; Harhoff et al., 2003; Trajtenberg, 1990), patent renewals (Schankerman and Pakes, 1985) and patent families (Lanjouw et al., 1998). Patent claims and the number of International Patent Classifications (IPC) have been used to measure the scope of the patents from both a technological (Lerner, 1994) and a legal (Kuhn & Thompson, 2017; Lanjouw and Schankerman, 2001) perspective, while information and the effect on technological diffusion based on forward and backward citations have been used to develop indicators of patent generality and originality (Trajtenberg et al., 1997). Also, patents have been used to measure technological complexity (Ivanova et al., 2017) and to capture the greening of inventive efforts (Dechezleprêtre et al., 2013). These indicators have been employed in a variety of empirical exercises, driven mostly by the strong underlying assumption that innovation is good for economic progress and for society as a whole (for a discussion see Giuliani, 2018).

However, we are now recognizing that innovation can have a dark side (Coad et al., 2020a; Biggi and Giuliani, 2020). The world is facing numerous problems related to sustainability and this is being accompanied by increased innovative efforts globally (for a discussion of the politics of innovation in the context of sustainability threats see, among many others, Ely et al., 2013). Both the UN 2030 Sustainable Development Agenda and the European Green Deal emphasize the importance of protecting our planet and human health from pollution and hazardous innovations - especially from "dirty" industries such as the chemical industry which has a long legacy of inventing substances or molecules that have proven to be particularly harmful to ecosystems and human health (Bartrons et al., 2016; Carlson, 1962; Jepson and Law, 2016; Johansen, 2003; Ma et al., 2011). The European Green Deal was formulated to ensure a toxic-free environment and is being supported by the European Commission's adoption in October 2020 of the European Union (EU) Chemicals Strategy for Sustainability. The Executive Vice-President for the European Green Deal, Frans Timmermans, stated:

> The Chemicals Strategy is the first step towards Europe's zero pollution ambition. Chemicals are part and parcel of our daily life, and they allow us to develop innovative solutions for greening our economy. *But we need to make sure that chemicals are produced and used in a way that does not hurt human health and the environment*. It is especially important to *stop using the most harmful chemicals* in consumer products, from toys and childcare products to textiles and materials that come in contact with our food. (emphasis added)

Calls for a toxic-free future have been made by several organizations including the World Health Organization (WHO) Inter-Organization Programme for the Sound Management of Chemicals, advocacy groups and civil society organizations worldwide. At the same time, the harms caused by exposure to toxic chemicals have become an international policy concern, which has been increased by the growing body of scientific evidence demonstrating the connection between chemical toxicity and health. For instance, there is more and more evidence emerging about the nexus between exposure – even at low levels – to certain pesticides and dominant contemporary diseases such as Alzheimers, autism and cancer (Jones, 2010; Pearson et al., 2016). In light of this evidence, the WHO and the International Agency for Cancer Research (IARC) keep chemicals under constant observation, while, since 2001, the Stockholm Convention - a United Nations treaty with 184 signatory parties – conducts periodic toxicity assessments of the class of chemicals known as Persistent Organic Pollutants (POPs). Between 2001 and 2017, 28 POPs received worldwide bans. These measures and other country- or regional-level regulatory initiatives to prohibit or limit the use of toxic chemicals, have laid the foundations for strategy to achieve a toxic-free world.

However, the historical bans under the Stockholm Convention show that although use of a particular molecule might be banned, the development of other potentially toxic molecules may be continuing. It is only in the future and, perhaps, after many years of in vivo and in vitro and epidemiological studies, that their toxicity will be proved. The POPs review committee is constantly reviewing new chemicals, which is evidence that companies and other inventive entities are continuing to invent and produce molecules and substances that are hazardous and show up on the radar of these authorities as toxic.

Academic research on the risks and policies related to chemical risks have for long pointed to the difficulties involved in implementing risk regulation, and the global and local regulatory mismatches in policies addressing the risks of chemical exposure. They also underline the lobbying power of large chemical companies and how it shapes the technological space and constrains the development of alternative pathways (among others see Lynn, 1986; van Zwanenberg, 2020; van Zwanenberg et al., 2013; van Zwanenberg and Millstone, 2015). A comprehensive overview of the functioning of banning bodies and the effectiveness of regulatory frameworks in this domain is beyond the scope of this research note. However, they call for a deeper understanding of what companies (and other inventing entities) are "cooking up" in their R&D labs. The point here is that, unless companies (or other inventors) enact strategies to shift away from toxic inventions, all regulatory efforts will be constantly challenged by new toxic discoveries. Therefore, we need to know *exactly* what kinds of discoveries - in terms of their potential toxicity - are being pursued in R&D labs. This has important implications, also, for studying, predicting and sharing knowledge about future threats. We are proposing the notion of patent toxicity, to capture or measure the extent to which a patent comprises "components" (in chemistry "compounds") that are toxic in one or more dimensions.

2. Assessing the Toxicity of Chemical Compounds

The toxicity of a chemical compound is measured along several dimensions or *toxicity endpoints*. A compound can be toxic to human health, for example, in terms of *mutagenicity,* which captures the degree to which the chemical causes cell mutations, or *carcinogenicity*, that is, its potential to cause cancer, or the whole spectrum of human health hazards including the functioning of the immune and neurological systems, liver damage, harm to the endocrine system, etc. (Wallace, 2012). Also, a chemical compound can be toxic to the ecosystem where toxicity endpoints can range, for example, from *bee toxicity* (i.e., the extent to which a compound harms the reproduction of bees) to *biodegradability,* which assesses how fast a compound biodegrades in the environment (for a full list of toxicity endpoints, see the OECD Guidelines for the Testing of Chemical[1]).

[1] https://www.oecd-ilibrary.org/environment/oecd-guidelines-for-the-testing-of-chemicals_72d77764-en

There are three ways to evaluate the toxicity of chemical compounds: *in vivo* experiments which assess the toxicity of a given substance directly on a living organism (e.g., an animal); *in vitro* experiments which assess toxicity on microorganisms, cells or biological molecules outside a living organism; *in silico* experiments which assess toxicity based on computer simulations. Compared to *in vivo* and *in vitro* experiments, *in silico* toxicity analysis is relatively new, but is becoming more accepted over time (Hemmerich and Ecker, 2020). *In silico* toxicity analysis relies on 'machine-learning software trained on masses of chemical-safety data which is increasingly considered so good at predicting some kinds of toxicity that it now rivals — and sometimes outperforms expensive animal studies' (Van Noorden, 2018, p. 163). In essence, it applies of computational chemistry methods to compare the structural and biological features of a chemical compound with the same or similar compounds whose effects have been established by prior *in vivo* or *in vitro* research. It has the advantage of being less costly than the other two methods and of avoiding the ethical problems of *in vivo* experiments. Because of these advantages, our measure of patent toxicity is based on *in silico* toxicity assessments.

3. Measurement of Patent Toxicity

We propose a methodological roadmap to measure patent toxicity (Figure 1), which involves three steps.

****Figure 1 about here*****

Step 1 includes search and extraction of chemical patents and their related chemical content. There are several databases that allow full-text searching and large-scale extraction of chemical content from patent documents. Licensed databases such as Clarivate Derwent Chemistry Resources (https://clarivate.com/derwent/), CAS SciFinder (https://scifinder.cas.org), and Elsevier Reaxys (http://www.elsevier.com/solutions/reaxys) are the most widely used sources in the industry, while open-access databases, such as SCRIPDB, provided by the Jurisica Lab at the Ontario Cancer Institute and the University of Toronto (http://dcv.uhnres.utoronto.ca/SCRIPDB) and SureChEMBL (https://www.surechembl.org), provided by the European Molecular Biology Laboratory (EMBL) are the two sources most frequently accessed by academic researchers and inventors. Regardless of the

source of the data, extraction of chemical patents results in a patent-compound association where compounds are specified according to their international structure identifiers, such as SMILES or InChiKey,[2] and their exact location in a specific section of the patent document such as the title, abstract, description or claims.

Step 2 involves use of computational chemistry techniques, such as Quantitative Structure-Activity Relationships (QSARs), to assess the potential toxicity of the compounds extracted from the claims listed in the patent documents.[3] QSARs are mathematical models which are used to predict any potentially undesirable or adverse effects of chemical compounds on human health and the environment, based on compounds' chemical structure (Cherkasov et al., 2014; Zimmerman et al., 2020). These effects or toxicity endpoints can be quantitative (e.g., LD50: lethal dose to 50% of tested individuals) or qualitative, such as binary (e.g., toxic or non-toxic) or ordinary (e.g., low, moderate, or high toxicity). In this study, we use VEGA HUB software (www.vegahub.eu) to predict the toxicity endpoints of chemical compounds. The VEGA HUB software was developed and is maintained by the Istituto di Ricerche Farmacologiche Mario Negri (IRFMN) as an open-source and large-scale library of QSAR models and is optimized following the European Legislation on chemical substances REACH.[4] The inputs for the VEGA HUB software are the international structure compound identifiers, and the output is a complete report containing toxicity endpoints and all the supporting information required for each compound (Benfenati et al., 2013). Based on a series of interviews with experts in toxicology and computational medicinal chemistry, we selected 22 out of 59 QSAR models provided by VEGA HUB, which best assess the two classes of toxicity of interest in this note: toxicity for human health and toxicity for the environment. The 22 selected QSAR models (see Table 1 Columns 2 and 3) provide an exhaustive representation of compound toxicity and their results can be interpreted easily, even by non-

[2] The Simplified Molecular-Input LineEntry System (SMILES) is a specification in the form of a line notation which describes the structure of chemical compounds. The International Chemical Identifier (InChiKey) is a textual identifier for chemical compounds, designed to provide a standard way to encode molecular information and to facilitate the search for such information in databases.

[3] We decided to focus on the claim section to account for the extent (i.e., the scope) of the protection sought in a patent document (Bekkers et al., 2020; Jayaraj and Gittelman, 2018; Kuhn and Thompson, 2019; Marco et al. 2019).

[4] The EU regulation REACH (Registration, Evaluation, Authorisation and Restriction of Chemicals) addresses the production and use of chemical substances and their potential impacts on both human health and the environment. In particular, it includes QSAR models as alternative tools for risk assessment of chemical substances.

experts in computational chemistry, since they are expressed mostly as binary outcomes (e.g., toxic or not toxic). To identify compounds toxic to human health, we consider five toxicity endpoints - mutagenicity, carcinogenicity, teratogenicity, steroidal activity and liver damage - by using a total of 17 QSAR models (some endpoints can be tested through more than one model). Similarly, we assess environmental toxicity through five QSAR models to test fish toxicity, algae toxicity, bee toxicity, sludge toxicity and ready biodegradability. Each QSAR model provides a different scale of possible results (e.g., a compound may be classified as mutagenic, suspected mutagenic or non-mutagenic). Based on the advice of toxicology experts, we adopt a *conservative* approach and, thus, do not consider a compound to be toxic if the model signals that the endpoint toxicity is only "possible" or "suspect" (Table 1, Column 4). Further details on toxicity endpoints and related QSAR models and their predictions, are provided by the authors upon request.

****Table 1 about here *****

Step 3 involves aggregation of the chemical compound toxicity scores at the patent level. Chemical patent claims can include a few or several compounds, sometimes several hundreds. These compounds may be active ingredients or other substances needed for to activate the product or process functions (e.g., reagents, catalysts, etc.). In some cases, a single patent could cover more than one active principle: for instance, the well-known commercial crop management product Round-Up, which was produced by Monsanto (now Bayer), includes both glyphosate (a broad-spectrum herbicide) and endosulfan (an insecticide). Patent claims also can include different combinations of active ingredients and other compounds, thus. providing alternative "formulae" for which the patent applicants seek intellectual protection.

Our proposed approach to measuring patent toxicity is based exclusively on the toxicity of the individual compounds present in the patent claim. It does not account for their interactions and synergistic or antagonistic effects (see the conclusion to this section). We compute four sets of measures for each type of impact on human health and on the environment:

Total Count Toxicity (TC_Tox), which counts the *total number of compounds* in the patent claim that are *classified as toxic* to human health or to the environment. As already discussed, we separate

human health from environmental impacts, and measure *TC_Tox* separately. $TC\_Tox\_HUMAN_p$ for human health is defined as:

$$TC\_Tox\_HUMAN_p = \sum_{c=1}^{C} D_c$$

where c (c=1, 2, …, C) are the compounds in patent p and D_c is a dummy variable equal to 1 if the compound c is categorized as toxic according to at least one of the five human toxicity endpoints (i.e. mutagenicity, carcinogenicity, teratogenicity, steroidal activity, liver damage).

$TC\_Tox\_ENV_p$ for the environment is defined as:

$$TC\_Tox\_ENV_p = \sum_{c=1}^{C} D_c$$

where c (c=1, 2, …, C) are the compounds in patent p and D_c is a dummy variable equal to 1 if the compound c is categorized as toxic according to at least one of the five human environmental endpoints (i.e. fish toxicity, algae toxicity, bee toxicity, sludge toxicity, ready biodegradability for environmental impacts).

Share Toxicity (S_Tox) is measured as the share of the patent claim's compounds that are classified as toxic either to human health or to environment, over the total number of compounds disclosed in the claim. Hence, we define the following measures:

$$S\_Tox\_HUMAN_p = \frac{TC\_Tox\_HUMAN_p}{C}$$

$$S\_Tox\_ENV_p = \frac{TC\_Tox\_ENV_p}{C}$$

Where C is the number of compounds reported in patent p.

Endpoint Toxicity (E_Tox) which is measured as the total number of toxicity endpoints detected on either human health or the environment, over the total possible number of toxicity endpoints in the patent.

$$E\_Tox\_HUMAN_p = \frac{\sum_{c=1}^{C}\sum_{e=1}^{E} D_{c,e}}{C * 5}$$

$$e = \{mutagenicity,\ carcinogenicity,\ teratogenicity,\ steroidal\ activity,\ and\ liver\ damage\}$$

$$E\_Tox\_ENV_p = \frac{\sum_{c=1}^{C}\sum_{e=1}^{E} D_{c,e}}{C * 5}$$

$$e = \{fish\ toxicity,\ algae\ toxicity,\ bee\ toxicity,\ sludge\ toxicity,\ ready\ biodegradability\}$$

where patent p includes c compounds (c=1,2, …, C) and $D_{c,e}$ is a dummy variable equal to 1 if the compound c is toxic for the endpoint e. The normalization is based on the theoretical maximum (i.e. 5* C).[5]

Toxicity Concentration (C_Tox) measures the extent to which toxicity is concentrated in one or a few compounds or is it detected equally across all the patented compounds, based on an adaptation to the Herfindahl-Hirschman Index (HHI). The two measures of toxicity concentration related to human health ($C\_Tox\_HUMAN_p$) and to the environment ($C\_Tox\_ENV_p$) are defined as follows:

[5] E.g., consider the patent p disclosing compounds A and B in the claims section. Compound A is shown to be toxic for mutagenicity, carcinogenicity, teratogenicity, steroidal activity and liver damage endpoints, scoring 5 in the human health toxicity class. Compound B is shown to be toxic for the carcinogenicity endpoint, scoring 1 in the human health toxicity class. As the total detected endpoints for patent p is 6 over two compounds, *E_Tox_HUMAN_p* is calculated as 6/(2*5) = 0.6 where (2*5) = 10 is the "theoretical" maximum, indicating that the patent is toxic for all the endpoints in the human health toxicity category.

$$C\_Tox\_HUMAN_p = \sum_{c=1}^{C} \left(\frac{\sum_{c=1}^{C} \sum_{e=1}^{E} D_{c,e}}{TOT\_END\_HUM} \right)^2$$

$$e = \{mutagenicity,\ carcinogenicity,\ teratogenicity,\ steroidal\ activity, liver\ damage\}$$

$$C\_Tox\_ENV_p = \sum_{c=1}^{C} \left(\frac{\sum_{c=1}^{C} \sum_{e=1}^{E} D_{c,e}}{TOT\_END\_ENV} \right)^2$$

$$e = \{fish\ toxicity, algae\ toxicity, bee\ toxicity, sludge\ toxicity, ready\ biodegradability\}$$

Where patent p includes c compounds (c=1,2, …, C) and $D_{c,e}$ is a dummy variable equal to 1 if the compound c is toxic for the endpoint e. *TOT_END_HUM* and *TOT_END_ENV* are the total numbers of human toxicity endpoints, and environmental toxicity endpoints respectively detected in patent p.[6]

4. Application

4.1. Patent selection

To illustrate our proposed methodology, we make an ad hoc selection of 10 patents covering universally recognized highly hazardous chemicals (hereinafter the target chemicals). The selection of these patents was made to include: (a) some of the most well-known hazardous chemical compounds, whose toxicity has been widely documented by different sources such as the Management Status Report the US National Toxicology Program (NTP, 2020), the US Environmental Protection Agency (EPA), the European Chemical Agency (ECHA) and the IARC; and (b) chemical compounds from each industry subclass in the Manufacture of Chemicals and Chemical Products class (NACE Rev. 2 - Statistical classification of economic activities). Based on these two criteria, for each sub-class we selected the following target chemicals:

[6] E.g., consider a patent p disclosing compounds A and B in the claim section. Compound A is shown to be toxic for mutagenicity, carcinogenicity, teratogenicity, steroidal activity and liver damage endpoints, thus, scoring 5 in the human health toxicity class. Compound B is shown to be toxic for the carcinogenicity endpoint, thus, scoring 1 in the human health toxicity class. As the total detected endpoints for patent p is 6 across two compounds, $C\_Tox\_HUMAN_p$ is calculated as (5/6)^2 + (1/6)^2 = 0.7222. The result (0.7222) denotes high concentration of human health toxicity due to a higher contribution of compound A.

(i) Manufacture of Paints. Varnishes and Similar Coatings. Printing Ink and Mastics: *(1) Methylene chloride* used as a solvent in paint strippers and *(2) Bisphenol A* widely used for the manufacture of plastic bottles and food storage items;

(ii) Manufacture of Pesticides and Other Agrochemical Products: *(1) Glyphosate* and *(2) Dichloropropene* – both pesticides used widely in farming;

(iii) Manufacture of Basic Chemicals. Fertilizers and Nitrogen Compounds. Plastics and Synthetic Rubber in Primary Forms: *(1) Oxirane* and *(2) Trichloroethylene* both used for the production of other chemicals such as polyester and polyethylene terephthalate (PET);

(iv) Manufacture of Soap and Detergents. Cleaning and Polishing Preparations. Perfumes and Toilet Preparations: *(1) Triclosan* a fumigant used in agriculture and to sterilize medical equipment and *(2) Para-dichlorobenzene* used as a disinfectant;

(v) Manufacture of Man-Made Fibres: *(1) Perfluorooctanesulfonic acid (PFOS)* and *(2) Perfluorooctanoic acid (PFOA)* both used to produce a wide range of products to protect against heat, chemicals and corrosion.

Table 2 reports the target chemicals, listed according to their industry classification, their trade names (i.e., the trademark or name used to trade the product containing the compound) and their main toxicological properties, defined according to the different sources.

****Table 2 about here*****

4.1. Patent search and retrieval

In Step 1 of the methodology depicted in Figure 1, we searched for and retrieved patents related to the target chemicals in the SureChEMBL database. The SureChEMBL includes all chemical patents filed at European Patent Office (EPO), the United States Patent and Trademark Office (USPTO), the Japanese Patent Office (JPO) and the World Intellectual Property Organization (WIPO) from 1976 onwards. SureChEMBL provides comprehensive compound-patent associations complemented by the exact location of the compound in the patent document (i.e., in title, abstract, claims or descriptions). It also provides s.c. SMILES or InChIKey information - the chemical compound structure international identifiers needed to conduct the toxicity analyses described in Step 2. Overall, the initial search yielded

135,420 compound-patent associations. For the purposes of our analysis, we selected one patent for each of the target chemicals, choosing the most recent patent filed by the original assignee (i.e., the assignee that discovered and patented the target chemical first)[7] or the first assignee that produced the target chemicals, based on a match performed using *The Merck Index* encyclopaedia (Paula, 2014).[8] We used the Derwent Chemistry Resource to double-check that the target chemicals are key "ingredients" in the selected patents and, thus, are at the core of the product or process described by the invention (tagged as "Use" in Derwent). Table 3 reports the compound structure identifier (InChIKey), assignee name and patent number for each target chemical.

Table 3 about here*

4.3 Toxicity analysis using QSAR models

In Step 2, we used the VEGA HUB software to run the QSAR models to predict the toxicity endpoints of the target chemicals included in the selected patents retrieved in Step 1. Note that, since toxicity was one of the criteria used to select the target chemicals its presence is not unexpected. In addition to referring to active substances – our target chemicals – the patent claims include multiple other chemical compounds, such as other active substances, reactants, solvents, and catalysts related to the patented chemical process or product. It is not unusual - especially in the pesticide sector – for these other chemical compounds to be as or even more toxic than the key ingredients (Beggel et al., 2010). In Step 2 we assess the toxicity of the patent based not just the selected chemical, but by considering all the compounds in the list of SMILES contained in the claim section.

Recall that we test five types of toxicity endpoints for each type of impact: (a) mutagenicity, carcinogenicity, teratogenicity, steroidal activity, and liver damage for human health impact (for a total

[7] We decided to analyze the most recent patent documents rather than the original patents because patent chemistry in older patent documents is not consistent with standard compound structure identifiers and, therefore, not in a suitable format for the toxicity analyses.

[8] *The Merck Index* is the most widely used encyclopaedia of chemicals, drugs and biological products and includes over 10,000 monographs on single chemical compounds. Monographs in *The Merck Index* typically contain - among other information - common and generic chemical names, chemical structures, trademarks and associated companies.

of 17 QSAR models), and (b) fish toxicity, algae toxicity, bee toxicity, sludge toxicity and ready biodegradability for environmental impact (5 models). This step is exemplified in Table 4, which presents extracts for the ten toxicity endpoint predictions for a selection of the compounds included in one specific patent claim. The patent considered is US20200236928 filed at the USPTO in 2019 by Bayer's Monsanto division, to protect the invention of a herbicide containing glyphosate as an active principle. Table 4 (Columns 2 and 3) show that the active principle glyphosate is classified as toxic for two endpoints – carcinogenicity (in 1 out of 6 models) and teratogenicity (in both models used to test this toxicity endpoints). We also examine the toxicity of all the other chemical compounds included in the patent claim. Table 4 reports only a selection of them and it can be seen that most score high for several toxicity endpoints. For instance, Bifenox is mutagenic, carcinogenic and teratogenic (Table 4, Columns 1, 2 and 3) while Fluoroglycofen is mutagenic, carcinogenic and toxic for the liver (Table 4 Columns 1, 2 and 5).

****Table 4 about here****

4. Patent toxicity indexes

We next calculate a group of patent toxicity indicators based on Step 3. Table 5 presents the target chemical (Column 1), patent number (Column 2), total number of compounds present in each patent claim for each target chemical (Column 3) and number of compounds classified as toxic for each endpoint grouped by type of impact (Columns 4 and 5 respectively, for health and environmental impacts). These data show that, in addition to the target chemicals, a large portion of the other compounds included in the patent's claims are also toxic. This provides a motivation and rationale for including all of the compounds to calculate the patent toxicity index.

****Table 5 about here****

In Section 3 we elaborated four categories of patent toxicity indexes – *Total Count Toxicity (TC_Tox), Share Toxicity (S_Tox), Endpoint Toxicity (E_Tox) Toxicity Concentration (C_Tox)*. Note that, in line with current methodologies for predicting the human health and environmental toxicity of chemical compounds, the overall toxicity of a chemical product derives from single-chemical studies (Monosson,

2005), which suggests that the presence of at least one toxic chemical compound should be the basis for considering the product described in the invention as toxic. Table 6 presents the patent toxicity indexes for each target chemical divided by type of impact (Health and Environment). This exercise is aimed, primarily, at showing how these indexes function and what they allow for. However, the index values are of interest in their own right since, essentially, they indicate (a) that in most cases the majority of the chemical compounds included in the patent claims are toxic to human health (and also but slightly less to the environment) and (b) that toxicity is not concentrated in the active ingredient, applies, also, to the other compounds.

****Table 6 about here****

5. Discussion and new research directions

A toxic-free world is one of the goals of the European Green Deal, and is part of the UN 2030 Agenda and a key objective of the WHO Inter-Organization Programme for the Sound Management of Chemicals. Several efforts have been made to put a stop to the use and production of chemicals, such as POPs - that threaten the future of the planet and its inhabitants' livelihoods. However, little is to be gained if some toxic chemicals are banned, but, simultaneously, others are being developed. We know little about the invention dynamics related to toxic chemicals, but we do know that the process of banning a toxic substance which is on the market, is complex and long (Coad et al., 2020b; van Zwanenberg, 2020). This suggests forcibly that we need to have a more accurate idea about what is being worked on in the chemical industry's R&D labs – based not on existing patent numbers or economic value, but an assessment of their potential toxicity.

In this research note, we combine patent analysis with computational toxicology to formulate a methodological roadmap to guide an investigation of the toxicity of the chemical compounds listed in patent claims, considering ten toxicity endpoints: (i) mutagenicity, carcinogenicity, teratogenicity, steroidal activity, liver damage for human health impacts, and (ii) fish toxicity, algae toxicity, bee toxicity, sludge toxicity, ready biodegradability for environmental impacts. For each type of impact, we proposed four patent toxicity indexes. We selected 10 of the most familiar toxic chemical inventions (Methylene chloride, Bisphenol A, Glyphosate, Dichloropropene, Oxirane, Trichloroethylene,

Triclosan, Para-dichlorobenzene, Perfluorooctanesulfonic acid and Perfluorooctanoic acid) and assessed their toxicity based on our proposed methodology.

This note provides a methodological contribution by proposing a novel combination of patent analysis and computational chemistry and developing a series of novel indicators to more accurately measure the potential "dark side" of innovation. We think more and better measures are needed to respond to the growing interest in understanding the causes and consequences of harmful innovations (Giuliani, 2018). So far, innovation studies have relied on technological classifications to identify "good" vs "bad" innovations, for example, green or brown innovations in the automobile industry (Aghion et al., 2016). We propose a new way to exploit patent information to investigate the technological trajectories of companies and other inventing entities, to assess whether they are investing in the generation of knowledge that is more (or less) likely to lead to a more environmentally and socially sustainable future.

However, our novel approach is only the first step in a bigger and longer-term research agenda. Also, we need to add some caveats. First, toxicology research suggests that chemical compounds can cause two types of interactions, such that the combined effect of two or more chemicals can be stronger (additive, synergistic, potentiating, supra-additive) or weaker (antagonistic, inhibitive, sub additive, infra-additive) than would be expected on the basis of dose addition or response addition (see, e.g., European Commission, 2012). This means that the combination of two or more chemical compounds can increase the overall toxicity of the final product or process – as in the case of additive or synergistic effects, for example, or can diminish it – as in the case of antagonistic effects, for example. While additive or synergistic effects are more frequent than antagonist effects, our proposed measures are not able to assess these interactions since computational models that account for the combined impacts of different compounds are not yet available. Also, in calculating our indexes, we do not weight each toxic compound by its toxic equivalent factor; this is an issue which requires further developments. Second, our approach uses computational chemistry methods and, therefore, is subject to the methodological weaknesses inherent in these methods (for a discussion, see Greene and Pennie, 2015). Third, we focused on inventions, but not all inventions become marketable products. Some countries – such as the EU member countries – have stringent procedures for screening toxic products and the EU REACH

regulation uses QSAR models to select out new chemical compounds if they are likely to be toxic based on extant knowledge. However, the regulations are less stringent elsewhere, and we know from prior research that some countries allow the use of highly toxic chemicals which are banned in other countries (Galt, 2008). For instance, multinational companies operating in multiple global markets may exploit their knowledge and profiting from given toxic chemicals for as long as possible by taking advantage of some countries' lax regulatory environments. Although some toxic chemicals are a threat only to the local environment, some travel, either through the air or embodied in products, with the result that use in one location can be hazardous for the whole planet. Because there is significant global fragmentation and ambiguity in the way toxic chemicals are used, traded and regulated, we believe there is a need for more transparency about where, when and by whom toxic chemicals are invented (or their property rights are protected) and consider that this is urgent to predict future hazards and to contribute to policy making in this area.

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Table 1: QSAR models and toxicity endpoints

(1) Impact on:	(2) Toxicity endpoint	(3) QSAR model	(4) Scale of possible results	(5) Criteria for classification
Human Health	1. Mutagenicity	CONSENSUS	Mutagenic, NON-Mutagenic	"Mutagenic" in one or more QSAR
		CAESAR	Mutagenic, Suspect Mutagenic, NON-Mutagenic	
		SarPy/IRFMN	Mutagenic, Possible NON-Mutagenic, NON-Mutagenic	
		ISS	Mutagenic, NON-Mutagenic	
		KNN/Read Across	Mutagenic, NON-Mutagenic, Non Predicted	
	2. Carcinogenicity	CAESAR	Carcinogen, NON-Carcinogen	"Carcinogen" in one or more QSAR
		ISS	Carcinogen, NON-Carcinogen	
		IRFMN/Antares	Carcinogen, Possible NON-Carcinogen	
		IRFMN/ISSCAN-CGX	Carcinogen, Possible NON-Carcinogen	
		Oral classification IRFMN	Carcinogen, NON-Carcinogen	
		Inhalation classification IRFMN	Carcinogen, NON-Carcinogen	
	3. Teratogenicity	CAESAR	Toxicant, NON-Toxicant	"Toxicant" in one or more QSAR
		PG	Toxicant, NON-Toxicant	
	4. Sterodial activity	IRFMN	Active, NON-Active	"Active" in one or more QSAR
		IRFMN/CERAPP	Active, Possible Active, Possible NON-Active, NON-Active, Not predicted	
		IRFMN/COMPARA	Active, NON-Active	
	5. Liver damage	IRFMN	Toxic, NON-Toxic, Unknown	"Toxic" in one or more QSAR

Table 1: Continued. QSAR models and toxicity endpoints

(1) Impact on:	(2) Toxicity endpoint	(3) QSAR	(4) Scale of possible results	(5) Criteria for classification
Environment	1. Fish toxicity	SarPy/IRFMN	Toxic-1 (less than 1 mg/l), Toxic-2 (between 1 and 10 mg/l), Toxic-3 (between 10 and 100 mg/l), NON-Toxic (more than 100 mg/l)	"Toxic-1 (less than 1 mg/l)", "Toxic-2 (between 1 and 10 mg/l)", or "Toxic-3 (between 10 and 100 mg/l)"
	2. Algae toxicity	ProtoQSAR/Combase	Toxic, NON-Toxic	"Toxic"
	3. Bee toxicity	KNN/IRFMN	Strong toxicity (lower than 1 µg/bee), Moderate toxicity (between 1 and 100 µg/bee), Low toxicity (over 100 µg/bee), Non Predicted	"Strong toxicity (lower than 1 µg/bee)", "Moderate toxicity (between 1 and 100 µg/bee)", or "Low toxicity (over 100 µg/bee)"
	4. Sludge toxicity	ProtoQSAR/Combase	Toxic, NON-Toxic	"Toxic"
	5. Ready biodegradability	IRFMN	Readily Biodegradable, Possible Readily Biodegradable, Possible NON readily Biodegradable, NON Readily Biodegradable, Not classifiable	"NON Readily Biodegradable" or "Possible NON Readily Biodegradable"

Table 2: Target chemicals: Industrial classification, compound name, trade name and main toxicological properties

Industrial Classification	Target chemical	Trade name or product containing them	Main toxicological properties of concern
Manufacture of Paints. Varnishes and Similar Coatings. Printing Ink and Mastics	Methylene chloride	MEC Prime; MECTHENE MC; MECTHENE PU	ECHA: Suspected to be Carcinogenic, Under assessment as Endocrine Disrupting; EPA: Likely to be carcinogenic to humans; IARC: Probably carcinogenic to humans
	Bisphenol A		ECHA: Toxic to Reproduction, Skin sensitising, Endocrine Disrupting; IARC: possibly carcinogenic to humans
Manufacture of Pesticides and Other Agrochemical Products	Glyphosate	Roundup, Rodeo, Pondmaster	ECHA: Causing serious eye damage and toxic to aquatic life; EPA: Not likely to be carcinogenic to humans; IARC: Probably carcinogenic to humans
	Dichloropropene	Telone	ECHA: Skin sensitizer, very toxic to aquatic life with long lasting effects ; EPA: probable human carcinogen; IARC: possibly carcinogenic to humans
Manufacture of Basic Chemicals. Fertilisers and Nitrogen Compounds. Plastics and Synthetic Rubber in Primary Forms	Oxirane	Ethylenoxid Reinst; Etyleneoxy (6CI); HEC; Makrogel 6000	ECHA: Carcinogenic, Mutagenic, Toxic to Reproduction, Under assessment as Endocrine Disrupting; EPA: Confirmed human carcinogen; IARC: Probably carcinogenic to humans
	Trichloroethylene	HI-TRI SMG; HI-TRI Solvent; NEU-TRI E; NEU-TRI L; NEU-TRI Solvent; THrichloroethylene Thymol stabilized	ECHA: Carcinogenic, Suspected to be Mutagenic, A majority of data submitters agree this substance is Skin sensitising; EPA: Carcinogenic to humans, IARC: Carcinogenic to humans (evidence for cancer is based on kidney cancer, limited evidence for non-Hodgkin lymphoma and liver cancer, as well as, various tumors in animals)
Manufacture of Soap and Detergents. Cleaning and Polishing Preparations. Perfumes and Toilet Preparations	Triclosan	Irgasan DP300	ECHA: Under assessment as Persistent, Bio accumulative and Toxic, under assessment as Endocrine Disrupting; EPA: probable human carcinogen; FDA: associated with hormone disruption in people
	Para-dichlorobenzene	1,4-DCB; DI-CHLOROCIDE; p-DCB; PARADI	ECHA: Suspected to be Carcinogenic; EPA: Possible Human Carcinogen; IARC: Possibly carcinogenic to humans
Manufacture of Man-Made Fibres	Perfluorooctanesulfonic acid (PFOS)	Scotchgard	ECHA: Suspected to be Carcinogenic, Toxic to Reproduction; EPA: adverse reproductive and developmental effects
	Perfluorooctanoic acid (PFOA)	Teflon, Stainmaster, Scotchgard, SilverStone	ECHA: Suspected to be Carcinogenic, Toxic to Reproduction, Persistent, Bio accumulative and Toxic; IARC: possibly carcinogenic; EPA: suggestive evidence of carcinogenicity

Table 3: Search strategy

Target chemical	InChIKey	Assignee	Patent Number
Methylene chloride	YMWUJEATGCHHMB-UHFFFAOYSA-N	Diamond Alkali and Stauffer (manufactured by Sanofi-Aventis, Bayer, and Solvay)	WO2011073703
Bisphenol A	IISBACLAFKSPIT-UHFFFAOYSA-N	Bayer and General Electric	US20120082833
Glyphosate	XDDAORKBJWWYJS-UHFFFAOYSA-N	Monsanto	US20200236928
Dichloropropene	UOORRWUZONOOLO-OWOJBTEDSA-N	Dow Chemical Company	US3914167
Ethylene oxide	IAYPIBMASNFSPL-UHFFFAOYSA-N	Union Carbide	US6372902
Trichloroethylene	XSTXAVWGXDQKEL-UHFFFAOYSA-N	Du Pont	US20120264667
Triclosan	XEFQLINVKFYRCS-UHFFFAOYSA-N	Invented at Ciba-Geigy (manufactured by BASF)	WO2015157261
Para-dichlorobenzene	OCJBOOLMMGQPQU-UHFFFAOYSA-N	Bayer	WO200226665
Perfluorooctanesulfonic acid (PFOS)	YFSUTJLHUFNCNZ-UHFFFAOYSA-N	Minnesota Mining & Mfg. (3M)	EP0605286
Perfluorooctanoic acid (PFOA)	SNGREZUHAYWORS-UHFFFAOYSA-N	Minnesota Mining & Mfg. (3M) (manufactured by Du Pont)	EP1431984

Table 4: Extract of the results of the toxicity analyses on US20200236928 patent assigned to Monsanto.

Compound name	Human health										
	(1) Mutagenicity					(2) Carcinogenicity					
	CONSENSUS	CAESAR	SarPy/IRFMN	ISS	KNN/Read-Across	CAESAR	ISS	IRFMN/Antares	IRFMN/ISSCAN-CGX	Oral classification IRFMN	Inhalation classification IRFMN
Glyphosate	**NM**	**NM**	**NM**	**NM**	**NM**	**C**	**NC**	**PNC**	**PNC**	**NC**	**NC**
Other compounds in the claim (selection):											
Bifenox	M	SM	M	M	M	C	C	C	C	NC	NC
Fluoroglycofen	M	SM	M	M	M	NC	C	C	C	NC	NC
2-chloro-6-nitro-3-phenoxyaniline	M	M	M	M	M	C	C	C	C	C	C
Oxyfluorfen	M	SM	M	M	M	NC	C	C	C	NC	NC
Naphthalic anhydride	NM	M	M	NM	NM	C	NC	C	C	NC	C
N-(4-fluorophenyl)-6-[3-(trifluoromethyl)phenoxy]pyridine-2-carboxamide	NM	NM	NM	NM	NM	C	C	PNC	C	NC	NC
2-[4-[4-(trifluoromethyl)phenoxy]phenoxy]propanoic acid	NM	NM	NM	NM	NM	C	C	C	PNC	NC	NC
2-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}phenoxy)propanoic acid	NM	NM	PNM	NM	NM	C	C	C	C	NC	NC
2-[4-(4-chlorophenoxy)phenoxy]propanoic acid	NM	NM	PNM	NM	NM	C	C	C	PNC	NC	NC

Note: Non-Mutagenic = NM; Suspect Mutagenic = SM; Mutagenic = M; P Non-Mutagenic = PNM; NON-Carcinogen = NC; Possible NON-Carcinogen = PNC; Carcinogen = C

Table 4: Continued. Extract of the results of the toxicity analyses on US20200236928 patent assigned to Monsanto.

Compound name	Human health					
	(3) Teratogenicity		(4) Steroidal activity			(5) Liver damage
	CAESAR	PG	IRFMN	IRFMN/CERAPP	IRFMN/COMPARA	IRFMN
Glyphosate	**TC**	**TC**	**I**	**PNA**	**NA**	**U**
Other compounds in the claim (selection):						
Bifenox	TC	TC	A	NA	NA	U
Fluoroglycofen	TC	TC	A	NA	NA	T
2-chloro-6-nitro-3-phenoxyaniline	TC	NTC	I	NA	NA	U
Oxyfluorfen	TC	TC	I	NA	NA	T
Naphthalic anhydride	TC	NTC	I	NA	NA	U
N-(4-fluorophenyl)-6-[3-(trifluoromethyl)phenoxy]pyridine-2-carboxamide	NTC	NTC	A	NA	NA	T
2-[4-[4-(trifluoromethyl)phenoxy]phenoxy]propanoic acid	NTC	NTC	I	PNA	NA	T
2-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}phenoxy)propanoic acid	NTC	TC	I	NA	NA	T
2-[4-(4-chlorophenoxy)phenoxy]propanoic acid	NTC	NTC	I	NA	NA	U

Note: TC = Toxicant; NTC = Non-Toxicant; A = Active; I = Inactive; NA = Non-Active; PNA = Possibly Non-Active; U = Unknown; T = Toxic

Table 4: Continued. Extract of the results of the toxicity analyses on US20200236928 patent assigned to Monsanto.

Compound name	Environment				
	(6) **Fish Toxicity**	**(7)** **Algae Toxicity**	**(8)** **Bee Toxicity**	**(9)** **Sludge Toxicity**	**(10)** **Ready biodegradanility**
	SarPy/IRFMN	**ProtoQSAR/Combase**	**KNN/IRFMN**	**ProtoQSAR/Combase**	**IRFMN**
Glyphosate	**NT**	**T**	**LT**	**NT**	**PRB**
Other compounds in the claim (selection):					
Bifenox	T-1	T	LT	NT	PNRB
Fluoroglycofen	T-1	T	LT	NT	NRB
2-chloro-6-nitro-3-phenoxyaniline	T-2	T	LT	NT	NRB
Oxyfluorfen	T-2	T	LT	NT	NRB
Naphthalic anhydride	T-2	NT	MT	NT	NRB
N-(4-fluorophenyl)-6-[3-(trifluoromethyl)phenoxy]pyridine-2-carboxamide	T-3	T	LT	NT	NRB
2-[4-[4-(trifluoromethyl)phenoxy]phenoxy]propanoic acid	T-2	NT	LT	NT	NRB
2-(4-{[5-(trifluoromethyl)pyridin-2-yl]oxy}phenoxy)propanoic acid	T-3	NT	LT	NT	NRB
2-[4-(4-chlorophenoxy)phenoxy]propanoic acid	T-2	T	LT	NT	PNRB

Note: T-1 = Toxic-1 (less than 1 mg/l); T-2 = Toxic-2 (between 1 and 10 mg/l); T-3 = Toxic-3 (between 10 and 100 mg/l); NT = Non-Toxic (more than 100 mg/l); LT= Low Toxicity (over 100 µg/bee); MT = Moderate Toxicity (between 1 and 100 µg/bee); NT = Non-Toxic; PNRB = Possible Non-Readily Biodegradable; NRB = Non-Readily Biodegradable; PRB = Possibly Readily Biodegradable

Table 5: Results of the toxicity analyses at the patent level.

(1)	(2)	(3)	(4)					(5)				
			Human health					Environment				
Target chemical	**Patent Number**	**# of compounds in patent claims**	# of mutagenic compounds	# of carcinogenic compounds	# of teratogenic compounds	# of steroidal active compounds	# of hepatoxic compounds	# of fish toxic compounds	# of algae toxic compounds	# of sludge toxic compounds	# of non-biodegradable compounds	# of bee toxic compounds
Methylene chloride	WO2011073703	16	3	3	1	0	0	0	0	0	7	1
Bisphenol A	US20120082833	13	3	12	8	1	0	7	1	4	4	3
Glyphosate	US20200236928	224	147	212	173	32	111	185	179	77	77	217
Dichloropropene	US3914167	9	8	7	4	0	3	6	4	0	2	0
Ethylene oxide	US6372902	15	4	12	11	2	0	2	3	3	6	3
Trichloroethylene	US20120264667	18	3	13	12	0	0	2	3	0	0	1
Triclosan	WO2015157261	76	13	53	39	0	2	12	12	12	46	44
Para-dichlorobenzene	WO2002026665	14	6	8	6	0	1	6	7	3	6	7
Perfluorooctanesulfonic acid (PFOS)	EP0605286	9	1	8	6	1	1	5	4	1	5	3
Perfluorooctanoic acid (PFOA)	EP1431984	196	94	156	144	17	24	120	79	55	71	126

Table 6: Measures of Patent Toxicity.

(1) Target chemical	(2) Patent Number	(3) TC_Tox		(4) S_Tox		(5) E_Tox		(6) C_Tox	
		Human health	Environment	Human health	Environment	Human health	Environment	Human health	Environment
Methylene chloride	WO2011073703	6	7	37,50%	43,75%	37,78%	40,00%	0,18	0,16
Bisphenol A	US20120082833	12	10	92,31%	76,92%	44,39%	46,02%	0,09	0,13
Glyphosate	US20200236928	221	219	98,66%	97,77%	36,92%	29,23%	0,00	0,00
Dichloropropene	US3914167	8	8	88,89%	88,89%	31,11%	6,67%	0,14	0,14
Ethylene oxide	US6372902	15	10	100,00%	66,67%	60,27%	65,63%	0,08	0,12
Trichloroethylene	US20120264667	16	4	88,89%	22,22%	48,89%	26,67%	0,07	0,28
Triclosan	WO2015157261	68	63	89,47%	82,89%	38,67%	22,67%	0,02	0,02
Para-dichlorobenzene	WO2002026665	10	8	71,43%	57,14%	30,00%	41,43%	0,11	0,14
Perfluorooctanesulfonic acid (PFOS)	EP0605286	8	7	88,89%	77,78%	8,75%	10,00%	0,15	0,19
Perfluorooctanoic acid (PFOA)	EP1431984	174	162	88,78%	82,65%	28,16%	33,16%	0,01	0,01

Note: TC_Tox = Total Count Toxicity; S_Tox = Share Toxicity; E_Tox = Endpoints Toxicity; C_Tox = Toxicity Concentration

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Figure 1: Procedure for the detection of the toxicity indicators.