

'A mechanistic interpretation, if possible': How does predictive modelling causality affect the regulation of chemicals?

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Abstract

The regulation of chemicals is undergoing drastic changes with the use of computational models to predict environmental toxicity. This particular issue has not attracted much attention, despite its major impacts on the regulation of chemicals. This raises the problem of causality at the crossroads between data and regulatory sciences, particularly in the case models known as quantitative structure–activity relationship models. This paper shows that models establish correlations and not scientific facts, and it engages anew the way regulators deal with uncertainties. It does so by exploring the tension and problems raised by the possibility of causal explanation afforded by quantitative structure–activity relationship models. It argues that the specificity of predictive modelling promotes rethinking of the regulation of chemicals.

Keywords

Predictive modelling, quantitative structure–activity relationship, causality, risk regulation

Humanity delegates active chemical substances to act not in the aseptic space of a laboratory but in a living labyrinth whose topology varies in time, where partial and circumstantial causalities are so intertwined that they escape any a priori intelligibility. (Bensaude-Vincent and Stengers, 1996: 263, quoted by Barry (2005: 57))

Introduction

The regulation of chemicals is undergoing drastic changes with the use of computational models to predict toxicity. In the EU, many chemical compounds (those produced between 1 and 10 tonnes/year) will fall under the scope of the registration, evaluation, authorisation, and restriction of chemicals (REACH) regulation by 2018.¹ Within this framework, industrials have to demonstrate the safety of a chemical prior to its market release. They have a major stake in developing predictive modelling acceptance for regulatory purposes, insofar as it significantly decreases the costs of toxicity experimentations. For this reason, the use of modelling and data-intensive techniques, such as for regulatory purposes, is increasingly routinised and standardised by regulators, the European Commission, and

the Organisation for Economic Co-operation and Development (OECD) alike, but also by national regulatory authorities. The use of modelling for regulatory purposes especially occurs through the development and implementation of 'QSAR models' (quantitative structure–activity relationship) (European Commission, 2006). Recently, the European Commission endorsed predictive modelling as valid regulatory evidence, hence defining an unprecedented legal use of 'Big Data'. So far, this particular issue has not attracted much attention, despite its major impacts on the regulation of chemicals.

There is a major stake in showing the ability of QSAR models to answer regulatory issues. For this purpose, 'causality' is pursued as a privileged option in order to answer the problem of control (Illari and Russo, 2014: 5), i.e. grounding policy decisions in knowledge as firmly established as possible.

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Could predictive modelling establish causal explanations? If so, how are QSAR models negotiated? In return, how does that affect the decision-making process in the regulation of chemicals? To explore these questions, we focus on one of the guidelines provided by the OECD. This particular guideline requires, in order to use QSAR models for regulatory purposes, a ‘mechanistic interpretation, if possible’. The ‘mechanistic interpretation’ refers to the imputation of a directed causality between a substance and its toxic activity. However, the ‘if possible’ points to a specific tension around the very possibility of carrying out such a causality *stricto sensu*, and it calls to enlarge the scope to other, larger forms of causality. This question matters when it comes to the use of modelling for the regulation of chemicals, because depending on which sort of causality will be enforced from a regulatory viewpoint, the requirements regarding the data generation and processing will diverge. Hence, ‘the data’ will not be the same according to whether a ‘mechanistic interpretation’ turns out to be possible.

In this paper, we unfold this tension and suggest that a ‘mechanistic interpretation’ seems to require a purification of the model, i.e. a directed causal explanation *within the model itself*. When the model proves unable to deliver it, then another sense of ‘causality’ emerges from actual regulation practice: that of regulatory authorities who strive to establish the conditions of validation for QSAR models to become workable for regulatory purposes. Whereas the first understanding refers to a causality *in abstracto*, which would be valid everywhere and every time (a ‘de-contextualisation’), the second refers more to a *situated* or *contextual* causality (a ‘re-contextualisation’) (Leonelli, 2014). What is interesting and to be learned from this case is that models are not fixed, immutable scripts that impose themselves on every situation. They cannot be expected to ‘speak truth to power’, as science used to (Hoppe, 1999). At least, QSAR models further challenge some previous achievements in boundary making between science and policy by reshaping the kind of evidence generated for regulating (Worth et al., 2014). In this respect, QSAR models open up a space for political negotiation: *it all depends* on which model you use for studying which material to what ends and purposes. Commenting on guidelines produced by the OECD, we explore the kind of causality enacted in scientific and regulatory practices with QSAR modelling.

In so doing, this study will contribute to the growing field of critical data studies, which aim mostly at not taking ‘data’ as given but instead as inserted at the locus of social, technical, and political configurations, considering the differences data make or can make in such configurations (Dalton and Thatcher, 2014).

Conversely, it will also analyse the notion of causality as it is at play with QSAR models and regulation processes, hence providing insights into the philosophy of computing and information (Floridi, 2011; Illari and Russo, 2014).

This paper relies on fieldwork I conducted between January and June 2015 within the framework of an experimental research project aiming to question the relevance of QSAR models for nanomaterials.² As part of this project, I attended several scientific meetings during which the construction of relevant data to feed a QSAR simulation was discussed (i.e. choice of reference substances, of physicochemical descriptors, and of relevant parameters). I conducted 12 semi-structured qualitative interviews between February and May 2015, with scientists developing experimental QSAR models for nanomaterials (Ecole des Mines Saint-Etienne) and a scientist from the Joint Research Center (JRC) of the European Commission; researchers working in the French industry (Sanofi in pharmaceuticals, Arkema in chemistry and materials); national regulators from the French regulatory authority (Agence nationale de sécurité sanitaire de l’alimentation (ANSES)), as well as international regulators from the European Chemical Agency (ECHA), from the OECD. All interviews were conducted orally, either through face-to-face meetings or through phone calls (on an average length of 1 h each). Each interview was recorded and integrally transcribed. Some of the people I interviewed are members of a QSAR management group that was set up by the OECD in order to coordinate the development and implementation of QSAR models and to promote its regulatory acceptability. All in all, the choice of interviewees was meant to provide me with a satisfying overview of different expectations and uses regarding QSAR models (scientists, industrialists, policy-makers). Although the interview protocol slightly differed according to my interlocutors, depending on their profession and relation to QSAR models, I nonetheless provide a representative interview protocol in Appendix 1.

In the following, I start by describing QSAR models and their definition. Then, I situate their use within current regulatory frameworks for chemical compounds (REACH) and the proliferating guidance provided by the OECD for an accurate use of QSAR models. Relying on my fieldwork, I come down to the central problem of causality. One of the OECD’s guidelines requests ‘a mechanistic interpretation, if possible’. This recommendation appears to suggest more than establishing a correlation between the structure of a chemical compound and its toxicity, but also some sort of causal relationship between them. This problem is particularly interesting to look at, as it is central to the kind of science that models can deliver, thus

redefining the kind of knowledge regulators deal with in decision-making processes. Furthering this analysis about causality, I then explore the hypothesis according to which models do not and cannot have the pretention to 'tell *the* reality' but rather to tell '*a* reality'. As such, they challenge the paradigm of 'evidence-based' regulation and the classic role of science as 'speaking true to power'. By requiring some forms of re-contextualisation, QSAR models call for an enlarged notion of causality, which affects the very practice of regulating.

QSAR models

QSAR models are usually defined as 'mathematical relationships between one or more quantitative measures of chemical structure (or physicochemical properties) and a biological activity' (Worth and Cronin, 2004: 703). In other words, QSAR models rest on the hypothesis that a link could be drawn between the description of a compound's structure and its 'biological activity', namely its potential toxic effects on the body or the environment. Therein lies an assumption that the toxic activity of a particular *virtual* chemical could be interpolated from the activity of another *actual* substance with similar physicochemical descriptors. As such, QSAR models are expected to draw a correlation between these two elements.

It takes many diverse processes to build and use QSAR models.³ To start with, it is important to give a clue about how QSAR models work in practice. The practitioner who wishes to predict the toxicity of a compound will have to choose a set of reference substances that share some descriptors, such as some features of the molecular structure, or its form. On this set of references, existing data must be provided, namely first-hand datasets issued from experimental protocols on the chosen particular substances. In the case of QSAR, datasets are physically distributed over a wide range of research centres and institutions, although they are often integrated (imported and duplicated) in widespread QSAR interfaces such as the OECD Toolbox or REACH (see below).⁴ The second step is to characterise the compounds about which the prediction will be formulated – these would have this or that shape, this or that feature, and could henceforth be linked with the set of references under several shared aspects.

Then, there is diverse QSAR software that allows for running analysis on these datasets to gather insights into the toxic activity of those new compounds. Some of the software is developed by private companies to fit their R&D purposes. Others are developed by a lively developer community that spans way beyond industry, including non-profit organisations such as Lhasa (which develops Derek, a widely used Open Source

QSAR software specifically directed towards predicting toxicity).⁵ Finally, regulators draft some specifications that integrate specific requirements for operating QSAR models for regulatory purposes and outsource the actual development of the software to private firms through public market procedures. For example, the OECD Toolbox – arguably the main, if not the only big enterprise of its kind – delegates the technical work to the Laboratory of Mathematical Chemistry in Bulgaria.⁶ The software will perform the prediction per se, i.e. gathering clues from existing data about the toxicity of a future molecule or chemical compound, based on a set of various criteria (its physicochemical description, but also its envisioned use and with respect to some specific effects). For this reason, the conditions of validation of the prediction lie with the software. A substantial form has to be filled out prior to running the simulation that specifies all these elements. This form elicits the conditions under which the model can be adequately used for regulatory purposes.⁷

QSAR models are widely spread in industrial and regulatory domains and sporadically used by non-governmental organisations. For instance, they have become routinely integrated in the practices of big pharmaceutical corporations since the late 1970s and early 1980s. Nowadays, these firms use QSAR insights for a 'pre-development' screening. For these firms, QSAR mostly helps them identify 'red flags' or areas one would not want to get into. For example, if a QSAR analysis shows that a virtual molecule could have genotoxicity, then the company will consider that over the infinity of potential molecules that could potentially be developed industrially; this particular one will not be worth the high costs of actual development. Models are taken up in a flux economy of chemistry – less and less in the linear development of a single molecule at a time, but instead in bulk processes of production through high-throughput and massive screening techniques (Manly et al., 2001). Barry (2005) showed that a start-up named ArQule used such screening methods as a way to generate added value, and it would then sell the promising molecules for further development to big corporations from the pharmaceutical sector (62).

Regulators somehow have to keep pace with such evolutions, and it is no surprise that regulatory bodies also use QSAR models to orient the decision-making processes. The American Environmental Protection Agency (EPA) developed and strengthened the first applications of QSAR models for regulatory purposes. It would carry this work out in cases in which data gathered from animal experimentation were already available to accurately delimit the restrictive conditions under which models could be used for regulation

(Demortain and Boullier, 2015). At the EU level, the European Commission took up the EPA's approach to models in 2007 through the enforcement of the REACH regulation. REACH frames QSAR models as an alternative to animal testing and expensive *in vitro* experimentations (European Commission, 2007). The directive operates within an overall framework in which the burden of proof (demonstrating that a substance is innocuous) belongs to industrials, not to the regulators – the ECHA together with the national regulatory bodies. The European Commission eases this demanding task for industrials that operate under resource constraints, just as the EPA does, which is the reason it strived to develop QSAR approaches in the first place (National Research Council, 2007).

In this respect, the demands for modelling differ significantly depending on whether it fits industrial or regulatory purposes. Industrials seek to avoid unnecessary spending in synthesising molecules or developing new chemicals that will not make it to the market, whereas regulators (OECD, ECHA) seek to determine if a chemical is safe enough for market authorisation. For this reason, QSAR has been routine for quite some time in R&D processes, whereas their use is still being consolidated in the regulatory domain. Industrials have to demonstrate the innocuity of a substance prior to market authorisation. In so doing, they have more and more incentives to use predictive modelling techniques, most often in addition to other evidence regarding a particular compound.

However, it would be a mistake to consider those two domains (industry and regulation) as strictly separated when it comes to QSAR models. Industrials have put know-how, research, and guidance into the development of those models for regulators. But as options are decided upon for regulating chemicals, industrials also learn to align to these choices, i.e. by running the same software and criteria of evaluation as the regulators. As one scientist from a regulatory body puts it: 'Of course they evaluate their own chemicals beforehand because they know the way in which it's going to be evaluated'. Therefore, the use and development of QSAR models in industry go hand in hand, nowadays, with the standardisation and validation criteria from regulatory authorities.

Operation for regulation purposes

At least three specific uses of modelling for regulatory purposes can be distinguished. The first and main one results from the development and adoption by the OECD of a 'QSAR Toolbox'. This tool centralises multiple datasets and seeks to provide means for standardising the conditions under which QSAR models can be used and evaluated. One of its main purposes, as one

member of the QSAR management group states, is to 'fill data gaps'. QSAR models are here useful to provide a panoramic, integrated view of the chemical's landscape and to distinguish categories about which toxicity information is lacking. This toolbox is crucial because it standardises the means of QSAR evaluation by using simple and widely used training sets, algorithms, and validation groups, whereas scientific expertise used to be over-specialised and too narrowly focused. A member of the OECD QSAR management group stated:

They invented the Toolbox which is a set of different similarity measures (...) for which you don't have this experimental data. This is the change in the way of thinking because those similarity measures are not very complex. They are not super robust, you know they are very basic things like simple ranges of properties, for example your substance needs to be with this range of molecular weight or it has to have this kind of water solubility.

Several interviewees pointed out that the OECD Toolbox tends to be increasingly used and recognised by some national regulatory authorities, hence standardising the regulatory work.

Second, QSAR models can play a determinant role to deliver market authorisation for substances with potential toxicity concerns for the environment. One of my interviewees who is well acquainted with regulatory practices stated that: 'Sometimes, there is just no analytical method for certain profiles of substances, from which we could get some "real data" or which at least appears right. If so, by lack of other means, we will use computer modelling' [prior to authorising] (my translation). Later on, this person added that, in such cases, he/she would tend to run 'worst-case scenarios'. He/she added that such a possibility would be considered only for 'environmental effects' and excluded if 'human health' was at stake. Whenever computer modelling is used, the validation process will be the main focus of investigation from regulatory authorities, which in turn drives reporting practices from industrials (see ECHA, 2016 [2010]).

Third, in most cases, or all of them insofar as human health is concerned, QSAR models can complement the scientific information gathered by means of experimental testing to comply with the regulation. In such cases, QSAR models can support or strengthen the administrative file for market authorisation. More generally, they can be used by regulatory bodies as an informative means to screen certain substances and identify potential threats early on, using the OECD Toolbox as a reference (see below, interview with the ANSES, 3 February 2015).

Because they can be used in different ways, QSAR models can best be described as instruments that perform an explanatory or predictive capacity. '*A public policy instrument constitutes a device that is both technical and social, that organizes specific social relations between the state and those it is addressed to, according to the representations and meanings it carries*' (Lascoumes and Le Galès, 2007: 4). At least, QSAR models can be considered 'instruments' insofar as they are expected to achieve public policy goals. Then, they entail a specific technical-political dimension, which rests with their ability to meet this regulatory aim. This renders their validation processes particularly challenging.

OECD guidelines

In order to validate QSAR models, guidelines have been developed within the framework of the OECD and REACH. Those guidelines contribute to fulfilling the goal of 'promoting mutual acceptance' of QSAR models in general across relevant regulatory authorities (OECD, 2007: 15).⁸ As such, they are situated within a series of activities of OECD, which pertain to the standardisation of modelling processes for policy-making purposes. This role, undertaken within the OECD since the early 1980s, has gone hand in hand with the definition of the OECD as an expert international institution that seeks, as a legal scholar puts it: 'to partition the technical aspects from the political' (Salzman, 2005: 203). Within this system: 'the contentious political decisions over whether to approve a chemical or product lies in the hands of regulatory agencies' (Salzman, 2005: 203). A particularly sensitive issue within the OECD is then the negotiation over what is to be left to member countries and what is the domain of the OECD intervention.

The OECD has been striving to demonstrate the regulatory relevance of QSAR models. For this purpose, the OECD has been elaborating guidelines for QSAR users and national regulatory bodies. These guidelines are crucial for the assessment of the validity of QSAR models. They were negotiated through the OECD coordination and were mostly formulated at a landmark workshop held in Setubal, Portugal, in 2002 (Jaworska et al., 2003). Guidelines are only one of the coordinating initiatives undertaken by the OECD, which also established a coordinating group on (Q)SARs, composed of members from national regulatory bodies and international institutions, as well as some firm representatives. The guidelines are the following:

To facilitate the consideration of a (Q)SAR model for regulatory purposes, it should be associated with the following information:

1. a defined endpoint;

2. an unambiguous algorithm;
3. a defined domain of applicability;
4. appropriate measures of goodness-of-fit, robustness and predictivity;
5. a mechanistic interpretation, if possible. (OECD, 2007: 14)

Guideline no. 2 is irrelevant for the question of causality, because by 'unambiguous' it simply means 'transparent', in the sense that the algorithm applied to modelling should be disclosed, which is not always possible, such as when a patent is at stake.

Guidelines no. 1, 3, and 4 are important to fully grasp no. 5, namely 'a mechanistic interpretation, if possible', which is our main point of concern in this paper.

Guideline no. 1 requires a 'defined endpoint' that relates to the biological activity of the chemical compound. Depending on which sort of impact one tries to unfold, different endpoints need to be set for the model to perform: 'Endpoint refers to any physicochemical, biological or environmental effect that can be measured and therefore modelled' (OECD, 2007: 14). In other words, setting the endpoint differentiates the kind of potential damages the model will be attempting to predict, either for 'skin irritation' or 'acute fish toxicity'.⁹ In this respect, it is closely related to the envisioned use of a compound in a given environment (e.g., skin creams or soluble products), which implies the exclusion, for the sake of the QSAR projection, of other uses, other kinds of effects, or other dimensions of the environment. Most of our interviewees indicate that QSAR models are able to deliver sound predictions on certain well-defined endpoints, but this is an exception – for example, reproductive toxicity (the impact on the ability of an organism to reproduce) is quite difficult to apprehend, as well as long-term exposures.

Guideline no. 3 requires delineating a domain of validity. It is a matter of defining the physicochemical descriptors that will characterise both current substances, for which data has already been generated, as well as compounds that do not exist yet. Therefore, this 'domain of validity' expands from existing data to QSAR projection and knowledge about future compounds. As such, the choice of descriptors defines the boundaries of a 'space', a set of coordinates that will match various substances within the same ensemble, hence delimiting a line inside the broad domain constituted by all chemicals. As Barry (2005: 62) points out: 'the quality of the models depends on the volume of *chemical space* they are able to operate within with some degree of reliability' (our emphasis). He adds that 'chemical space is not Euclidian or Newtonian but instead a relational space'. Indeed, it is through the definition of the domain of applicability that a

link is established between different substances – through the choice of certain descriptors over others. QSAR models can deliver accurate projection only if this link between current and future compounds can be firmly established.

From within that ‘chemical space’, the toxic activity of future chemical compounds will be interpolated from other substances that present similar properties. This is the very purpose of QSAR models: to delineate under which conditions an accurate predictive ‘coverage’ of a chemical can be assured. The OECD (2007: 35) asserts the following rule: ‘If a (Q)SAR is based on physico-chemical descriptors, the interpolation space (i.e. its coverage), defined by its descriptors, should be characterized’. Does this or that chemical fall under this area of coverage that a particular model delineates? From there, based on a few *in vitro*/*in vivo* tests, predictive modelling intends to interpolate the potential toxicity of whole groups or families of chemical compounds by means of computer simulation. This is the very stake of QSAR modelling, as one of our interviewees working in the pharmaceutical industry puts it:

Let’s say that I have 100 molecules in mind out of which I’ll be able to synthesise only 10. How am I going to prioritise according to the toxic effects? (...) Using models proves interesting when you select the points about which you can predict something accurate. That implies, on the one hand, that new points and new molecules revolve in the same chemical space, that is, that the model is valid. On the other hand, we try to avoid that the model is so well trained for a certain set of determined molecules that it can only make predictions for the molecules inside the model.¹⁰

It is therefore an original approach, which does not deal with all the chemicals (the whole) nor with each chemical in itself (the part), but rather with a ‘cohort’ of chemical compounds constituted through the choice of descriptors. This is the particular goal of regulatory processes known as the ‘grouping of chemicals’ or ‘read-across’ to establish such transversal categories (OECD, 2014). To do that, they realise two distinct operations. The first is a classical regression. It is a correlation that can be established between two substances which are henceforth considered similar, according to the choice of a set of descriptors. The second is more relevant for regulatory purposes and operates a classification. The classifying algorithms will carry out a bulk analysis of future compounds and assign them to a specific category according to their properties. The specific operation will be to include such a future entity in a group of chemicals to which it will then belong.

Guideline no. 4 intends to establish the ‘robustness’ or ‘goodness of fit’ for QSAR models. This is precisely the locus of trial for those models. Here, the questions asked are: Does the model hold? Does the link hold? Is it firmly established? In other words, what these guidelines propose is a list of conditions for building a robust linkage between a substance as characterised by a choice of descriptors and its biological activity, that is its toxicity. To assert the strength of the link, classical ‘stress tests’ in statistics will be applied, and what will be put to test is the model’s ‘internal performance’ and ‘external performance’ (OECD, 2007: 42). What is interesting here is that this criterion of robustness is in no way absolute. Instead, it refers to the quest for a local optimum between a model that is too narrowly focused on one very precise situation (very accurate but not very relevant) and one that is too loosely focused (possibly relevant but not very accurate for decision-making purposes). The OECD stresses that a ‘suitable balance’ must be established between those ‘two extremes’ (OECD, 2007: 42).

In this section, I provided an overview of the inner operation effectuated by QSAR models in general. I showed that the main aim of a model is to classify future substances and to establish firm correlations between similar compounds and their toxicity. Such models thus engage in a multi-variable setting that depends upon the choice of one or many descriptors and endpoints. It is understood that neither one nor another of these descriptors encapsulates the ‘reality’ of the chemical at stake, but instead one or several of its *relevant dimensions*, for the purpose of adequately regulating the future plausible uses of that chemical. This reveals just how much models need contextualisation in order to operate for regulatory purposes.

According to an ECHA official we interviewed, this requirement is far from sufficiently met in current practices. This official considered that some companies ‘would not really care about the context in which they are using this model’. He further mentioned the difficulty in using endpoints that would be ‘too complex’, such as those related to long-term exposures and/or carcinogenic effects. Another interlocutor from the chemistry industry stated that ‘ecotoxicity’ had to be ruled out of the field of application of QSAR modelling, for the resulting ‘correlations (...) [we]re way too weak’. In other words, a balance must be reached between ambiguous predictions and actual robust tests, and endpoints must be narrowed down to enable regulatory decision-making. Although regulation is not about certainty, it is certainly about reliability, and that explains the trickiness of the process. I now discuss more specifically this question of causality by examining guideline no. 5 in detail.

The problem of causality

The use of QSAR models for regulatory purposes presents the problem of causality at the crossroads between data and regulatory sciences. The OECD's guideline no. 5 requests 'a mechanistic interpretation, if possible'. This recommendation goes a step further than establishing a mere link, in the sense that the very structure of the substance somehow *implies* the biological activity. Of course, this is not a direct, straightforward implication, but rather an implication that is retraced back to a chain of damages caused to the organism, from the molecular and cellular levels to tissues and flesh. The underlying hypothesis of this sort of causality is that

normally, in order to have [an adverse effect] on the organism or population level, everything starts at the molecular level; something happens at the molecular level, then on the cellular level, then on the tissue level. Then, you can see the impact of this on the population. For example, if you are affecting the reproductive capacity of individuals, you will see the effect on the population later on as well, yes? (ECHA official, interview)

This is called the 'adverse outcome pathway', defined by Burello (2013: 2) as 'the result of an exposure to a material [that] can be described as a sequence of linked events, from a direct molecular initiating event to an adverse outcome at a biological level of organization'. That pathway retraces the adversity of a chemical or of a molecule, step by step, towards organisms and populations. While this echoes the more general aim of QSAR models (establish a link between a chemical structure and its 'biological activity'), here the 'mechanistic interpretation' refers to the possibility of establishing the pathway by which a chemical causes damage from the tiniest elements of the body (molecules, cells) to the body at large. To do that, it is necessary to rely on an extensive literature review and multiple datasets and to fill gaps in the existing knowledge. According to one ECHA official:

[OECD is] trying to put together all the mechanistic data that we know from pharma investigations, from different small *in vitro* assays that are really, you know, just designed to detect certain features, and they are trying to build full pathways [i.e.] full chains of reactions that lead from something small at the molecular level to something big — that show some adversity at the organism level.

Does the toxicity *derive directly* from the structure? Here, what matters is the 'discovery of underlying causal relationships' (OECD, 2007: 66). Henceforth, what is looked after is not only a predictive capability

of QSAR models but also an explanatory capability. Although this explanatory capability is not entirely straightforward, it derives from the possibility of scaling up the 'adversity' of a particular compound to an organism. Hence, it tends to establish a precarious, long, and complex chain of adverse events, but a chain nonetheless. In this sense, the kind of causality is not strictly linear but could be said to be 'directed'; it is more of an indication, a view upon a sequence of events that tends to cause adverse effects for the organism. In fact, 'currently, we don't have models that are able to emulate full organisms, and this is something that people need to take into account' (interview with a member of the OECD QSAR management group). Interestingly, the OECD added the phrase 'if possible' because it sees the evolution of these models as 'an iterative process involving the statistical exploration of data, hypothesis generation, and hypothesis testing' (interview with a member of the OECD QSAR management group). In other words, establishing models that perform something is an iterative procedure, which needs some refinements and experimentations.¹¹

This tension underlies the problem of control, which is crucial for regulation processes. As I argued before, this dimension is already present in the functioning of QSAR models, since they formulate predictions upon which decision-making processes can be based, which has to do with the control of the variables (endpoint and domain of applicability). But this problem of control is reinforced when it comes to actually delivering a 'mechanistic interpretation'. Then what needs to be conformed with and aligned to the models is the world itself (Illari and Russo, 2014). In such a configuration, models could tell something about the future compounds themselves, because they would apprehend them with such precision that their exact activity could be inferred from their inner structure, which in turn implies that this structure would be perfectly known and mastered. The idea is to establish a directed causal bond between a structure and its activity. In this perspective, a cause could be known with enough precision to accurately predict one or several of its effects. This sequential perspective is challenged by the intensive use of computers, data, and models in trying to formulate predictions.

It thus appears that guideline no. 5 is unlikely to be met, except in some specific cases, but then at the expense of very precisely defining the boundaries of the material and the kind of effects examined. Hence, modelling simulations provide guidance through complex situations. As Illari and Russo (2014: 15) explain:

(...) simulations, whether run on computer or physical models, are neither experimental nor observational, but something much more complex. Scientists create an

imitation system that is capable of having something like experiments run on it, and use that imitation system to probe features of the target system; it can then be tried out in some way on the target system—perhaps by suggesting new experiments, or by directing new observations.

QSAR models establish correlations between physicochemical descriptors and biological activities, and any ‘mechanistic interpretation’ would be an incidental event.

This raises the question of how to deal with uncertainties in regulatory processes, and that is by no means a new problem in itself. Yet it is interesting to unfold it in the early stages of development of QSAR models for regulatory purposes, before the models and their inner indeterminacy could be ‘naturalised’ in some sort of ‘algorithmic regulation’ chimera (see Morozov, 2014). If the notion of causality at play does play a role in this situation, it is rather as some ‘cherry on the cake’. Economists would call it a ‘positive externality’; others would say ‘models with benefits’. In short, a causal explanation is *neither sufficient nor even necessary for the model to perform*, although it might occasionally strengthen it.

When models challenge the practice of regulating chemicals

We have seen that QSAR models tend to establish quasi-experimental orders of relationships through correlations and that a ‘mechanistic interpretation’ is not needed in order for them to operate from a regulatory perspective. There is a long tradition of using all sorts of different predictive models for environmental policy and regulation. It is understood that each case is specific and drives different uses of different types of models. None of them actually require absolute certainty to perform. As Fisher et al. (2010: 272) point out in the framework of environmental regulation: ‘models cannot be expected to deliver certainty. They cannot generate facts and they cannot generate definitive answers’, but they are definitely used for evaluation or assessment processes. As other forms of regulatory-relevant knowledge, models are simplified representations of reality, rendering them actionable for policy-makers.

In the realm of chemicals, this can become problematic. Since the early controversies about the appropriate evidence to mobilise in order to introduce regulatory constraints, public institutions have adopted a language of separation between risk ‘assessment’ and risk ‘management’, with the former related to scientific examination and the latter considered policy and, more generally, value issues (see Jasanoff, 1987, 1990). The choice of what counts as valid knowledge for regulatory

purposes is by definition controversial (Demortain, 2013). In this perspective, providing a ‘mechanistic interpretation’ can be seen as an attempt to provide a kind of ‘evidence’ robust enough for policy decisions. Indeed, QSAR approaches render very explicit the fact that risk assessment is again a matter of political choices. Whereas dose–effect toxicology could be construed as a stabilised black box neatly separated from policy decisions (albeit permanent controversial), QSAR modelling makes it necessary to re-ask the question of the appropriate evidence. Choices have to be made to produce tentative new knowledge and to reshape the renewed problems posed by the relationship between this new knowledge and decision-making processes.

Within such a situation, the ways in which QSAR models affect regulation are not unidirectional. Models take place in a regulatory landscape that they help shape. The OECD (2007), for instance, states that models challenge regulatory categories: ‘A model that gives highly accurate predictions for narrow chemical classes *that are not covered* by the regulatory inventory of interest would be of questionable value’ (40). In that sense, what is happening is a co-production of models and regulation, in which models take up and challenge some pre-existing categories while affecting them. In so doing, QSAR models also question the very basis on which the existing regulatory system is based, as well as the ways in which it could potentially be redefined.

QSAR models require dealing with multi-variables relations. For this reason, they need to account for the particular choices of one or several descriptors and of one or several endpoints. None of these choices might ‘exhaust’ the combinatorial possibilities in the sense of encapsulating reality as a whole (Deleuze, 1992).¹² It depends on many factors: the chemical at play; the way it has been characterised, with its effects considered; its further combination with other substances; the length of exposure; unknown reactions when it is inserted into new environments; and so on. Instead, through computer modelling, what is definitely reached for is *a* reality, not *the* reality (Atlan, 2011). Models, Hacking (1983) argues: ‘are intermediaries’; they suppose that a phenomenon is true (i.e. the toxic activity), and they suppose that the theory they are grounded in is also true (the structure–activity relationship). Hence, they *mediate* those two orders of reality: ‘siphoning off some aspects of real phenomena, and connecting them, by simplifying mathematical structures, to the theories that govern the phenomena’ (217). QSAR models, just like every model, appear to be reductionist in that sense – and this is something that the OECD itself acknowledges clearly (OECD 2007: 15).

Models such as QSAR models acknowledge the partiality of the connections they can establish between

different worlds or milieus and potentially toxic chemicals. 'Models come in varying degrees of abstraction' and 'can be constructed in a variety of ways' (Morgan and Morrison, 1999: 4). But the important point remains that such a partiality does not prevent the effectiveness of the model. Simply, the sort of causality implied here has much more to do with a 'rationale of variation' (Russo, 2009). However, whereas the regulation of chemicals used to be grounded in 'a model of reality' (Jasanoff, 1987), it might well be that each specific use of a QSAR model will produce its own specific reality, perhaps turning the idea of 'reality' itself into a moving target. There is something going on there as the active production of complexity that renders difficult the validation of QSAR modelling, which depends on many variables, let alone the establishment of a causal pathway that ties together damages to a molecule to broader adverse effects on the organism.

Along the way, QSAR remodels not only the very idea of 'causality' but also the way decision-making needs to adjust to such tentative realities crafted by models. Models adopt a sort of incremental approach that tends towards the truth by approximations (Hacking, 1983); it takes going back and forth from the models to its effects, and therein lies the potential truthiness of a model. 'If there is any truth around, it lies in the approximation, not in the background theory' (Hacking, 1983: 219). And here it appears clearly that it is a form of experimental endeavour rather than the causal application of a theory. This experimental endeavour is well visible in the many choices at stake in the definition of endpoints, datasets, and other technical features of QSAR. That these choices are connected to regulatory choices is a reason the OECD guidelines state that they have to be made explicit, without attempting to pre-determine them. But it also renders more acute a boundary issue at the heart of the public regulation of risk, in which 'science' and 'politics' are constantly intertwined.

The 'mechanistic interpretation, if possible' reminds us that, insofar as possible, the best way to proceed consists in establishing a form of causal explanation. However, the 'if possible' reflects a strong tension between the art of establishing correlations, which is what QSAR models do, and the very possibility of finding causal relationships between the structure of a particle and its toxicity, as in an adverse outcome pathway. This is why the validation process will probably become so dramatically important in the future regulation of chemicals, because it renders explicit all the features and specifications under which the knowledge provided by the model has been constructed as valid for each specific situation.

QSAR modelling suggests considering an emerging regime of evidence. At the interplay of computational

modelling and existing regulatory categories, it suggests new institutions able to recognise a world made of irregularities, or regularities that can hardly be explained in a straightforward way, that is, meanings of causality that are disaffiliated from certainty but, at most, inscribed in long and complex chains of events. Barry (2005) argues that modelling makes the modes of existence of molecules proliferate through the delimitation of chemical spaces. To paraphrase him, I could suggest that in the same way, by producing new groups (through grouping of chemicals) and new families of compounds, what could actually happen is the creation of new 'regulatory spaces'.

Just like chemicals, regulation as put on trial by models will have to delineate its own 'regulatory space'. With this shifting regime of evidence, regulatory bodies have to make explicit the conditions under which they enable decision-making, such as the definition of the domain of applicability and contextualised boundaries within which a particular decision can actually deliver what it is supposed to deliver – safety from toxic compounds. In so doing, one can hypothesise that the political spaces where these models are developed and hoped to be used as relevant regulatory tools would be different from the institutions in which positivist evidence-based processes form the basis for policy interventions – and in which the very notion of 'evidence' itself is insufficiently problematised (see, e.g., Timmermans and Berg, 2003). Technical arenas, such as the OECD QSAR management group, the ECHA in charge of REACH, or the JRC (a research centre of the European Commission active in the definition of appropriate QSAR models), might well become sites of particular political interest if the regulatory interest for QSAR is developing.

Conclusions

In this paper, I focused on the use of QSAR models for regulating chemicals, especially through the development of the OECD guidelines. In particular, I insisted on the one that requires '*a mechanistic interpretation, if possible*'. This last guideline underpins a new regime of evidence characterised by the impossibility to stabilise 'a model of reality', but it might instead carry forth 'a reality', provided that the conditions of validations are carefully made explicit and closely put on trial by regulatory bodies. Yet, I argue that the very use of predictive modelling could open up new modes of apprehending chemicals that are rooted in experimentation. Through QSAR modelling, both the chemical substance and the regulatory process need to go through a process of contextualisation.

QSAR models need to be used not as a one-size-fits-all tool, valid for all purposes, but as a political tool

that underpins a learning process, i.e. determines contexts of use and levels of public acceptability, and directs the attention towards potential chemical threats and hazards. Bensaude-Vincent and Stengers (1993) argue that chemical entities are not fixed once and for all but instead should be considered as ‘informed materials’, that is materials that cannot be separated from the world they are entangled in. In the same way, QSAR models could not be fetishised as purely performing instruments, but rather point out to the necessity of contextualising both the model and its subsequent uses for decision-making purposes. This could be called ‘informed modelling’. This is a form of ‘regulatory chemistry’, in which models and chemicals would not be considered independently but instead grounded in a thick context of use. ‘The chemist is interested in the fact that the properties of atoms and molecules vary considerably depending on the form and circumstances of their association with others’ (Barry, 2005: 56). Just like Barry’s chemist, the ‘modelling regulator’ would learn to deal with the uncertainties inherent to multi-variables analysis and would be sensitive to the adjustments and caution required by a ‘variation rationale’, thus rendering the notion of ‘evidence’ as in ‘evidence-based decisions’ problematic.

Such an evolution would have ontological consequences. Not all of that is indifferent from the data viewpoint; depending on how far regulatory processes can follow that path, different sets of demands and requirements and, eventually, different datasets will be generated, asking different questions to different families of molecules. Since the spectrum of covered realities is potentially unlimited, it would not make sense to talk about ‘the data’ but about ‘some data’ or ‘datasets’, understood as partial and limited. There would be consequences for the molecules themselves, since their informational environment would be dramatically affected by models. As for the regulatory authorities themselves, they would hereafter embrace uncertainties about the material, not deny them; they would not take physicochemical descriptions as invariant but instead as transformed through association with other political stakes.

Supplementary material

The supplementary files are available at <http://bds.sagepub.com/content/3/2>

Notes

1. Regulation (EC) no. 1907/2006 of 18 December 2006 concerning the REACH, consolidated version of 1 June 2015.
2. This research project is entitled ‘Risk assessment for Oxide nanoparticles: social impact and establishment of Quantitative Structure-Toxicological Activity Relationship’ (ROQSTAR). It was funded under the ‘Ressourcement Carnot M.I.N.E.S 2013’ from October 2014 to September 2015.)

3. This roughly summarised process has been extensively addressed through my interviews.
4. Collecting data about existing chemicals, i.e. about their physicochemical properties and toxicity, is an important goal of REACH regulation.
5. <http://www.lhasalimited.org/products/derek-nexus.htm> (last accessed 13 April 2016).
6. <http://oasis-lmc.org/> (last accessed 13 April 2016).
7. The detailed analysis of these specifications would not fit in this paper. However, the interested reader can refer to the reference guidance document from the OECD (2007).
8. REACH specifies a more restrictive series of conditions in order for QSAR results to be used instead of classical testing. The following conditions are cumulative: (1) results are derived from a (Q)SAR model whose scientific validity has been established, (2) the substance falls within the applicability domain of the (Q)SAR model, (3) results are adequate for the purpose of classification and labelling and/or risk assessment, and (4) adequate and reliable documentation of the applied method is provided, see European Commission (2006: 202), Annex XI, 1.3.
9. For a full list, see OECD (2007: 23).
10. My translation. The interview was conducted in French, 5 February 2015.
11. That being said, the document stresses right after that that it is only a matter of time before models can explain everything. Of course, this sequential view and this particular teleology could be discussed, but this is out of scope.
12. Deleuze states that the ‘whole of possibilities’ can never truly be exhausted, since new possibilities necessarily arise along the way.

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