**Governing anticipation through flexibility. The use of models for the regulation of chemicals.**

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**Introduction**

As the use of models is increasing within regulatory bodies, it is important to grasp both the empirical practices of producing and using them, and their political meaning. At stake here is the possibility of identifying the characteristics of a way of governing anticipations that would be based on models. In this paper, we engage in such an exploration by focusing on models developed to predict the potential risks of chemicals. These models, called “Quantitative Structure-Activities Relationship” (QSAR), are based on statistical correlations between a set of descriptors (e.g. chemical composition, crystalline structures…) and a set of physicochemical properties, including potential toxicity. They are developed using a limited number of substances that serve as reference points, so that the properties of other chemicals could later be predicted by the model, according to their proximities to the reference points. QSAR models have been promoted by regulatory agencies for over twenty years, but have been recently gaining momentum in Europe, in the wake of the REACH regulation. As the regulation on chemicals is becoming more constraining on private companies, usual experimental approaches raise many concerns (which are lengthy, costly and often requires animal testing).

Based on the analysis of the relevant documentation, interviews with scientists and regulators, as well as the ethnographic observation of a recent research project attempting to developed QSAR models for nanomaterials, this paper provides the preliminary elements for describing the mode of governing anticipation that emerges from the use of such models. We contend that QSAR approaches offer empirical examples to identify a mode of governing anticipation based on flexibility, understood at the epistemic and political levels.

In section 1, we show that the use of QSAR models defines new categories for chemicals expected to be regulated. This definition is more than just constructing new categories, since these categories are not clear cut, but inherently fuzzy and necessarily flexible.

In section 2, we show that the use of QSAR models in regulatory institutions redefine the traditional boundary-making process characteristic of the government of toxicological risk. As validation processes and models are simultaneously crafted, and technical black-boxes are constantly re-opened, the scientific and administrative approach to QSAR for the sake of regulation is also flexible.

Thus, and building on works in STS that have studied the coproduction of epistemic and political orders (Jasanoff, 2004), the discussion of the use of models for regulation making that we propose in this paper offers insight into the analysis of flexibility as an engine for both the production of convincing scientific evidence and legitimate regulatory decisions.

**1. Flexible objects of government**

***1.1. New objects of government shaped through QSAR models***

The problem of drawing categories for chemicals is an acute one. Regulators need to isolate entities so as to render them governable, that is, shape entities fit for performing a form of control. This problem becomes interesting when it comes to mold categories for entities that do not exist yet, or only as the result of an anticipation. Such an anticipatory uptake changes the ways and means of producing categories through the use of models, and henceforth has consequences on the very regulatory regimes at play.

The logic of QSAR models is inherently tied to category-making processes. As we will show, by definition, such models are made purposely to “group” chemicals on the basis of their identified similarities, along methods which are qualified as “read-across” ones.

Hence, what is at stake here is not just a matter of defining the objects but also of regulating them, i.e. rendering them amenable for regulatory purposes. It has been long shown in the field of Science & Technology Studies (STS) that the very definition of technical entities in regulatory bodies has both epistemological and political consequences. For instance, Sheila Jasanoff has clearly demonstrated that the *description* of GMOs goes along with *prescriptions* about how they should be regulated (Jasanoff 2004; see also Latour 2015). That way, a claim about what the physical world *is* also entails to some extent the appropriate policy choices to undertake. Such a “constitutional work” is particularly visible when considering the operations through “objects of government” (such as regulatory categories describing GMOs or chemicals) are constructed (Lezaun, 2006), and is currently carried out about chemicals within the framework of the REACH regulation at the European level.

Within REACH, companies need to submit a dossier for each chemical substance they produce or use, in which they demonstrate their ability to evaluate and control potential hazards. For a company putting a chemical on the European market, the question is whether or not the chemicals it aims to register is equivalent to an existing one. For the European public administration, particularly the Helsinki-based European Chemical Agency (ECHA) in charge of the management of REACH, the problem is to evaluate whether or not companies can identify a given chemical to others about which toxicological data already exist. Here, the problem is to group chemicals in categories characterized by similar levels of risks.

Facing the complexities and conflicts that arise while drawing categories, the European Commission has so far adopted an approach of “regulatory precaution” based on a case-by-case approach. Under such an approach, chemicals are considered in isolation one from the others, therefore specific toxicological data should be generated anew. This leads to the endless examination of cases and subsequent multiplication of them, since an infinite variety of parameters can be used to differentiate among substances, e.g. atomic composition, crystalline structure, optic properties, etc. (Boullier and Laurent 2015).

The way QSAR models could overcome such limitations is made particularly salient in the case of nanomaterials. So far this regulatory case has been marked by a twofold shortcoming, i.e. case-by-case vs. arbitrary categories. On the one hand, actual regulatory authorities would endorse the EC’s limited case-by-case approach we just discussed. But on the other hand, the European Parliament, representative of Europe’s people or its general interest, would go for very large definitions. For example, in the case of nanomaterials, it would arbitrarily set a defined size limit for delineating the “nanoness” of new materials (1 to 100 nm). Doing so, it would elude any possibility to come to terms with the peculiarities of the materials themselves.

The project in which we have been involved was explicitly designed as a way of escaping this quandary through the use of QSAR models and to overcome this twofold limitation. The aim of the project was to build a predictive QSAR model for nanomaterials, so that it could be possible to group them in several groups, each comprising substances with similar risk profiles. By defining more precisely “profiles” of risk, it would become possible to generate new categories which cut across the whole (made of general definitions) but which also escape the form of nominalism at play when dealing with one single particle at a time (case-by-case).

QSAR methods propose to do such grouping operation, based on physical or chemical descriptors, and associated expected properties. Andrew Worth, a specialist of QSAR methods at the Joint Research Center (JRC) of the European Commission, explains it as follows:

*According to Chapter 3 of the OECD Manual for Investigation of HPV chemicals, a chemical category is defined as:*

*. . .a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity. These structural similarities may create a predictable pattern in any or all of the following parameters: physicochemical properties, environmental fate and environmental effects, and human health effects.*

*One particular way of expressing the “structural similarity” between different chemicals is to define a structural fragment (SAR) that the chemicals have in common, and a particular way of expressing a regular or predictable pattern is to define a QSAR that links the different chemicals on the basis of physicochemical properties. It therefore follows that SARs and QSARs have a role to play in the formation and rationalisation of chemical categories.*  (Worth et al., 2004: 340)

Accordingly, QSAR methods would allow to group chemicals according to common characteristics that would generate similar physicochemical properties – including those linked to potential hazards. As such, these methods offer ways of grouping chemicals without endlessly separating among them (on the one hand), or creating general and arbitrary criteria (on the other hand).

***1.2. Flexible categories: choosing descriptors and endpoints***

In the same paper, Andrew Worth states that “however, there is no consensus on how exactly (Q)SARs should be used to define and justify chemical categories.” That there is no consensus pertains to both scientific and political difficulties, in a way typical of issues related to risk regulation, only increased by the particularities of using models.

These difficulties relate to the actual conduct of QSAR methods and the choice it entails. These methods require that a series of “descriptors” are chosen first, using experimental data gathered with a limited set of reference materials. These descriptors are meant to describe the chemicals at stake in relevant ways – “relevant” in that they have consequences on physicochemical properties one expect to predict. This is the second choice required by the QSAR methods. One needs to identify “endpoints”, that is, the properties expected to be predicted. Choosing descriptors and endpoints requires that one decide about the appropriate measuring instruments, the right criteria for description, as well as the endpoints considered relevant for regulation making. This is not an easy task, nor is it standardized. Rather, it usually proceeds through trials and errors.

When examining how these operations are conducting, the case of nanomaterials can serve as a magnifying empirical lens since all the issues related to the construction of categories (and the high hopes that they carry) are present, only in an even more pressing manner. There are indeed many uncertainties about how best to describe nanomaterials in way that could come to grasp the connections between potential descriptors and endpoints. An official at ECHA describes the nanomaterials situation as follows:

*Because on the top of everything which I told you already, how complex the hazard assessment is by nature, you have to add one additional element that is how size matters, which means how the size of the particles are affecting the toxic properties. (…) The question itself is very complex and then you have to take into account many additional factors on top of everything else. And some of those factors we don’t even have yet fully studied. For example do you know what – how exactly – what is the ratio or the – how the size of a certain particle will for example affect the membrane penetration interaction and so on? We don’t have a direct study which can – we know more or less some thresholds, yeah that something which is smaller than a certain size will easily penetrate the membranes than if something is bigger maybe it will not penetrate the membranes but it can be still by active mechanism uptake and so on, but this is only – we don’t have yet full information to really properly model it.* (interview, ECHA)

This quote is telling, as it clearly states the unease shared by regulators and scientists about how to choose appropriate descriptors for nanomaterials – “appropriate” to the extent to which they would have important consequences for their hazard profile. The stakes that arise behind the choice of descriptors are hereby intrinsically regulatory and thus political.

During the project we followed, the selection of descriptors was a crucial and much discussed step. The following discussion (between A, B and C, three members of the project) is about whether or not to quantify the form of the substances being used to build the model, and then about what criteria to select in order to differentiate among substances:

1. *Descriptors are not all quantitative… how will we do for the shape of substances?*
2. *So far, what I’ve done is that I have typed the number for each dimension. So if I see “first dimension equals 6”; “second dimension equals 6”; “third dimension equals 300”, I know that it’s a little stick, shaped as a cylinder. (…) Because all our particles have cylindrical symmetry.*
3. *But you could also do, “if it’s a sphere then 1”, “if it’s a cylinder 2”, “3 is a lump”, etc.*
4. *Right, I could separate among all those… Well, what we need to differentiate is among those that are agglomerated or not. (…) There are three or four shapes that we feel like separating, when looking at the pictures.*
5. *We could differentiate among 4 types: isotropic isolated nanoparticles, isolated sticks, isolated bars, and formed aggregates. (…)*
6. *Then there is an ambiguity with boehmite, because boehmite is really bars. But we see sticks, because the bars are superposing themselves – like tiles. Somehow it’s bars and sticks in the same time*
7. *Yeah right, you could do both… but then the question is “what does the cell see?”. And for me, the cell sees sticks. (…) We just take the situation according to the cellular cell, and then it’s not bars. I agree that for a chemist, it’s bars.*
8. *What the chemist sees, and what the biologist sees…*
9. *But there’s no truth in itself here, we choose descriptors from the viewpoint of the cell…*
10. *That’s why when you look at the OECD descriptors, some of them are from the viewpoint of the environment, or from the viewpoint of the river.*

This somewhat long dialogue offers a window into the practical process through which developers of QSAR models choose descriptors. Here, the descriptors being discussed are related to the “shape” of the substances, and what various shapes scientists “feel like separating” among one another, so that a substance on which the model will be used will be described as “particles”, “bars”, “aggregates”… Then the question relates to the number and type of these descriptors of shape. Looking into how this question is dealt with, one can make two remarks.

First, as seen from this exchange, isolating descriptors is a process based on a variety of inputs, including references to guidelines produced by international organizations, considerations about what will make a difference in toxicology effects, and expectations about the potential effects on potential endpoints.

Second, the choice of descriptors is tightly connected to the choice of endpoints. The later part of the dialogue above is about the “viewpoint” of the cell, the environment or the river. If the endpoint is cell toxicity (as it is in the previous excerpt), then the descriptor has to be chosen “from the viewpoint of the cell”. If the endpoint is aquatic toxicity, then the viewpoint will be that of the river. Accordingly, the choice of appropriate descriptors is tightly connected to the potential endpoints one need the model to provide, themselves directly related to regulatory constraints (are the required tests related to cell toxicity? Or to environmental toxicity in aquatic environment?). These two phenomena have consequences. First, the list of descriptors might vary greatly among QSAR models. Second, there is a fundamental uncertainty about the appropriate choice of them, and, consequently, about the categories emerging from the grouping of substances according to descriptors. Getting back to the dialogue above, the project might lead to group substances according to their shapes as “bars” or “sticks”, yet will do so in the context of an interrogation about cell toxicity.

***1.3. Flexible categories: trials and errors, negotiating accuracy***

The dialogue above relates to the early step of a QSAR model development project, at the stage when descriptors and endpoints are chosen, that is, even before any statistical correlation between descriptors and endpoints have been undertaken. Yet exploring statistical correlations between descriptors and endpoints is an iterative process during which the list of descriptors might vary. A person in charge of using QSAR for a French pharmaceutical company explained during an interview that the process of building statistical correlation (that is, the model itself) was characterized by “trials and errors”. If she observed “no answer” from a series of descriptors, that is, that they did not impact the value of the endpoints in statistically significant ways, then she would deduce that they were not relevant, would eliminate them, thereby reducing an initial long list to just a few parameters.

That the choice of descriptors is based on trials and errors also means that defining the domain of applicability of the model itself is also based on trials and errors. For the objective of a QSAR development project such as the one we studied is to craft the model using known substances in order to enable prediction of potential toxicological properties for other substances, according to their proximity to the ones used to construct the model. For instance, the project we studied used among other substances various kinds of boehmites, working on the hypothesis that these different varieties would offer sufficient information (for instance related to the effects of shape) to situate other nanomaterials according to their proximity to the reference substances.

Yet two problems might arise at this point. The first one is called *overfitting* by QSAR specialists. It means that the model is so tailored to the substances being used to construct it that it is unable to provide any significant information about any other substance. In a case of overfitting, any substance that is different from those used to produce the statistical correlation would be too different for the model to perform. In order to avoid overfitting, QSAR specialists need to build statistical correlations that are *not too accurate*, in order for the model to be usable for new entry data. Overfitting requires that one uses a limited number of descriptors so that other chemicals can fit within the model. Yet this raises a second problem, namely that of using too few descriptors for the model to build significant statistical correlation. For a correlation to arise, one needs a minimal (yet impossible to know in advance) number of descriptors, various enough for statistical relationships to emerge.

Avoiding the problem of overfitting and that of non relevance requires that QSAR practitioners, such as those we interviewed, proceed with caution, and, re-invent their methods for each dataset of chemicals used to build models. For them, the objective is to build accurate models, yet not too accurate that they would be unable to predict anything for new chemicals. To do so, they might process by trials and errors about the list of descriptors, and also about the software tools they use to build correlation. QSAR practitioners we interviewed indeed stated that they might have a variety of software, and adapt their uses according to the responses they get and the correlation they manage to produce.

At this stage, it is useful to get back to Andrew Worth’s remark that there is no consensus on the use of QSAR for defining chemical categories. This is not surprising considering the situatedness of the choices to make (what descriptors? What endpoints? What models?), all depending on regulatory options, available scientific data, and on the personal experience of the people involved in the production of models. This flexibility in the production of QSAR models directly impacts the potential future categories of chemicals based on QSARs. The variety and situatedness of the choices to make imply that categories might be permanently reworked and are, at any case, extremely flexible.

One can wonder whether this flexibility is a first step in the development of models that would ensure the construct of robust categories basing stable objects of government. In other words, are we observing the early stages of a process that will eventually be similar to other regulatory approaches to toxicological risks?

Part of the answer to these questions can be found in the previous descriptions. The choices of descriptors have to be reworked for each model, and depend on endpoints that hinge upon regulatory choices. The construction of significant statistical correlation that could be used to predict potential hazards of chemicals not used to build the models themselves require a subtle play with accuracy that has to be re-experimented each time. Accordingly, the flexibility of category making in an inherent characteristic of QSAR approaches. As such, there is no hope of stabilizing categories once and for all using these models. They require more of an *ad hoc* approach, simply which operates at the “group”, “category” or “family” level, instead of case-by-case approaches which can handle one specific particle at a time.

But is it then possible to standardize the tools and methods? Here, the role of the OECD as a provider of international expertise and would-be standardization organization could be central, considering what the international organization has done with the standardization of hazard assessment tests. Indeed, the OECD has been active in the production of expertise about chemical testing since the early 1980s, thereby defining itself as an expert international institution able, as a legal scholar puts it, “to partition the technical aspects from the political” (Salzman, 2005: 203).

The OECD has developed a so-called “QSAR toolbox” meant to provide ready-made tools for the grouping of chemicals using QSAR. Within the European institutions, many initiatives are undertaken in order to clarify what an appropriate use of QSAR could be within the REACH regulation. For instance, the ECHA published a report in 2008 entitled *Guidance for grouping of chemicals*, which discusses the ways in which QSAR can be appropriately used in the European regulatory context. These initiatives, meant to provide technical expertise about the use of QSAR for regulatory reasons appear to offer stabilized methods. The question here pertains to the sheer possibility of standardizing tools and methods for the making of categories that are meant to be flexible. How is it possible to make modeling through QSAR an acceptable instrument for the regulation of risks, sufficiently standardized that it can convince of its ability to predict potential hazards?

The next section explores this question. We will see that the answer is ambivalent, as the process through which QSAR models could be made into workable and transportable regulatory black-boxes is flexible. Ultimately, we show that the use of QSAR rewrites basic principles at the heart of the traditional government of risks, such as the definition of stable regulatory categories (cf. the previous discussion), the identification of stable validation procedures, and the construction of technical black boxes. Instead, we show that QSAR goes with a government of anticipation based on flexibility (of categories, of tools and methods, of administrative formats).

**2. Flexible scientific and administrative procedures**

The regulation of risks requires the production of public proofs able to convince regulators, industries and citizens that scientific evidence allow lawmakers to constrain or authorize. As STS scholars have shown, producing public proofs in this domain has relied on boundary-making processes, such as the ones through which “risk assessment” and “risk management” are isolated from one another, both in the conduct of scientific work and in the institutional organization of expert agencies and regulatory institutions (Jasanoff, 1990). These boundaries are permanently at stake, not less because of the inherent value choices at the heart of risk assessment – regarding, for instance, the working hypothesis, the choices of priorities of studies, or the management of scientific uncertainties[[2]](#footnote-2). The flexibility of category making processes within QSAR approaches and the variety of scientific disciplines mobilized (material scientists, toxicologists, computer scientists…) suggest that QSAR models impact the production of boundaries between “assessment” and “management”, between “expertise” and “policy decisions”. We discuss this impact in this section from the analysis of two related processes:

- first, we describe attempts at stabilizing validation processes for QSAR models that end up being permanently (albeit not entirely) re-crafted;

- second, we discuss the ambiguous attempts at turning QSAR approaches into technical black-boxes for regulatory decisions.

***2.1. Crafting validation processes and models simultaneously***

Models, in QSAR approaches as in other fields, need to be validated to convince scientific and regulatory audiences of their predictive value. Defining rules for the validation of models is a way of building public proofs based on agreed-upon validation processes that work as technical black-boxes separated from regulatory and/or policy decisions. As such, validation is an operation that might offer a practical way of separating risk assessment from risk management.

In the case of QSAR, the validation of models has been subjected to intense scrutiny, since it is a condition for models to be used as basis for regulatory decisions (such as restrictions on the circulation of certain categories of chemicals on markets). That the discussion about validation processes has been lasting for years and is still ongoing at the time of writing is significant of an inherent difficult in stabilizing validation criteria. QSAR specialist Andrew Worth explained in a 2004 paper that one could isolate “principles” of validation that could be standardized from “procedures” that would need to be flexible and adapted to each model:

*It is useful to distinguish between the principles of validation, which should ideally be accepted at an international level, and different procedures of validation, which provide different ways of implementing the principles in a practical process. In fact, it is widely agreed that there should be some flexibility in the validation process, so that individual validation exercises can be tailor-made to take into consideration the state of development of individual tests or models.* (Worth et al., 2004: 3)

The distinction Worth proposes here is interesting, since it suggests re-introducing a boundary between standardized “principles” of validation, and adaptable “procedures”, the former being produced through international (possibly “technical”) agreement, and the latter being crafted according to local scientific and regulatory specificities.

The initiatives undertaken at the international level seem to follow Andrew Worth’s 2004 suggestion. At the OECD, the recognition that there were significant variations across countries about the use of QSAR came early, and raised the issue of the harmonization of validation approaches:

*The regulatory use of (…) (Q)SARs varies considerably among OECD member countries, and even between different agencies within the same member country. This is partly due to different regulatory frameworks, which impose different requirements and work under different constraints, but also because an internationally harmonised conceptual framework for assessing (Q)SARs has been lacking. The lack of such a framework led to the widespread recognition of the need for an internationally- agreed set of principles for (Q)SAR validation. The development of a set of agreed principles was considered important, not only to provide regulatory bodies with a scientific basis for making decisions on the acceptability (or otherwise) of data generated by (Q)SARs, but also to promote the mutual acceptance of (Q)SAR models by improving the transparency and consistency of QSAR reporting.*(OECD, 2007: 15)

Harmonizing QSAR validation processes eventually took the form of general principles agreed upon at the OECD. These principles 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).

The production of such principles within the OECD seems to follow Andrew Worth’s suggestion that “principles of validation” should be accepted “at the international level”. These principles indeed offered a way of ensuring international agreement about QSAR validation processes. Yet they had to do so without entering the domain of regulation making, which was that of sovereign policy choices, outside the scope of OECD intervention. For the OECD intervention to be acceptable, as that of a provider of “apolitical” international expertise, QSAR validation principles had to be framed in a general way. Consequently, no considerations about relevant endpoints could be acceptable, since the choice of endpoints is directly related to regulatory decisions. This consideration is made explicit in the OECD’s self-description of its principles of validation, meant to ensure a level of generality that would not cross the boundary between international expertise and sovereign regulatory choices. Consequently, these principles are not enough to practically validate models, and might be ambiguous (this is particularly the case for the 5th principle, “mechanistic interpretation, if possible”, which attempts at re-introducing a form of causality that is not statistical (Thoreau, forthcoming)).

Considering what validation processes are in international arenas, it is not surprising that the European institutions need to re-isolate principles and procedures at the European level in order to define a validation approach. Thus, Andrew Worth draws a difference between the role of the European Centre for the Validation of Alternative Methods (ECVAM) and regulatory bodies:

*As a consequence of this distinction, it is important to devise principles and procedures for the scientific validation of (Q)SARs, which are separate from the considerations and procedures necessary for regulatory acceptance. This distinction marks the difference between the role of the ECVAM, which is responsible at the EU level for the independent validation of (Q)SARs, and the roles of regulatory bodies, which will need to make decisions on the acceptability of (Q)SAR models and estimates for specific regulatory purposes.* (Worth et al., 2004: 349).

At the OECD, the five principles are defined in such a way that they do not enter the domain of regulation making, characterized notably by the definition of endpoints. Within the European institutions, the separation plays out somewhat differently, since endpoints are defined within the European regulation, and this cannot be ignored by ECVAM as it crafts its “principles”.

Consequently, validation principles within the European institutions can be more operational than the OECD ones. Yet more difficulties arise. Validating QSAR models can be carried out processing the data that have been used to construct the statistical correlations (this is described as “internal validation”), or other data (e.g. chemicals of known risks, on which the model will be run, and its predictions checked against the known risks of the tested chemicals). The latter approach is called “external validation” and is deemed more robust for regulatory choice by QSAR specialists (Gramatica, 2007). Yet external validation also requires additional data, and additional testing to check whether the predictions according to the model are correct, and yet another validation process for the choice and use of these additional data.

When the diversity and permanent evolution of statistical tools are added to the picture, the conclusion, drawn by Andrew Worth himself, is that the validation process cannot be “set in stone”:

*There should be nothing to fear from this process, since no conclusion on the validity of an experimental test or a (Q)SAR model is ever set permanently in stone—scientific and technical developments should always be taken into account. The question will always be when should the validity of a (Q)SAR (or a test method) be reviewed, either due to an adaptation of the model (test) itself, or because a new assessment (e.g. statistical) method is developed, or because new information (e.g., test data) becomes available.* (Worth et al., 2004: 356)

In practical terms, this means that the standardization of validation processes can only take the form of general principles, leaving the practical conduct of validation to the particularities of the regulatory and technical situations at stake. Depending on the type of chemicals and models, internal or external validation processes will be used, and in ways that will differ from one case to the next. Thus, QSAR practitioners and regulators need to re-question the appropriate validation methods for each new situation. This later point is clearly visible when considering for instance the “modular approach” undertaken by ECVAM:

*Traditionally, ECVAM validation studies were prospective validation studies, because a wide range of information was needed to properly assess the validities of the tests being considered. However, there is an increasing need to validate tests for which pertinent information is already available, but for which some additional information is needed to produce a complete dossier on test validity. In such cases, it may not be necessary to perform fully-fledged prospective validation studies, but to design targeted studies that are aimed to complete the dossier of information. For this reason, ECVAM is currently developing a so-called “modular approach” to validation, as a means of introducing the necessary flexibility in the validation process, while safeguarding internationally agreed principles of validation.* (Worth et al., 2004)

As category-making based on QSAR is inherently flexible, so is the validation process. Accordingly, the 2008 guidelines proposed by ECHA about the grouping of chemicals based on QSAR do not propose to standardize the validation methodologies, but mean them to be permanently discussed by the actors involved, and regularly adapted. Ultimately, it can be argued that this means that the use of QSAR for regulatory decision cannot take the form of the mobilization of a ready-made instrument about which there could be unambiguous consensus on its scientific validity:

*Even though computer-based estimation tools are becoming increasingly available, these tools are intended to facilitate the process of (Q)SAR acceptance and cannot substitute the need for expert judgement and dialogue between industry and authorities. The use (Q)SAR predictions in an automatic way, without considering validation results, regulatory purpose and use of WoE judgements is not recommended. Having said that, on the basis of current experience, it is difficult to give detailed guidance on how to use (Q)SAR estimates for regulatory purposes. Indeed, it is debatable to what extent it will be possible to codify accepted practise in terms of rules-of-thumb, although some attempts must be made along these lines.*

*The approach proposed is that experience in the regulatory use of non-testing data should be obtained by following a learning-by-doing approach, with the learnings being documented as examples for reference purposes. In this way the possibilities for enhanced use of non-testing methods in general under REACH will be optimised whilst avoiding long bureaucratic and formal adoption schemes.*(ECHA, 2008: 26-27)

A quote such as the previous one offers a striking difference from what is expected from expert and regulatory institutions in charge of the government of risk. Rather than stabilizing a boundary between a technical expert expected to provide reliable risk assessment upon which sound regulatory decisions could be undertaken, the objective here is to maintain enough flexibility so as to adjust any regulatory process to the particular situation at stake, knowing that no standardization of the method can be in sight. Thus, the approach is a “leaning by doing”, which implies that several cases are documented, both to produce additional models and offer insights into how they are used for regulatory purposes.

***2.2. The ambiguity of black-boxing***

As validation is a never-ending process, the specification of which going hand in hand with the development of the models themselves, a way of reducing variety in the use of models could be provided by black-boxing processes – whereby some elements (such as calculation tools) are agreed upon and can circulate.

The OECD “toolbox” can be seen as an attempt at blackboxing. It is being developed in coordination with ECHA and was originally conceived as a way of delegating the construction of an instrument that could systematize the grouping of chemicals based on statistical correlations, and according to endpoints that would be chosen by the user of the toolbox. It would then offer yet another model, but possibly more robust and widely accepted that other ones. The implication of ECHA in the development of the toolbox was described as such by an official during an interview:

*(In 2008…), ECHA decided to support OECD in the development of the project. So after a proof of concept phase, ECHA funded the second phase of development and now we are funding already a third phase of development which is for the next four years. So basically we have been investing for six, almost seven years in this tool already. (…) we are not only investing money but we are investing our expertise and our expectations as well, which means that we are also sharing our experience with QSAR and (… exploring) how we could make the Toolbox nicer, more robust, easier and so on.* (interview, ECHA)

In doing so, the delegation of the production of the toolbox to the OECD is a way for ECHA to ensure that a component of a regulatory approach is developed independently from regulatory choices, so that it could travel easily across various cases. This is made explicit in the internal organization of work at the OECD. The same person from ECHA re-stated in a way the importance of the science/policy boundary, in order for a technical black-box to be developed independently from policy considerations, as he made the following comment:

*So this is something which we are doing, but (…) this is not like we are making decisions together with our colleagues from OECD, no we have – the project itself has a Management Group which is responsible for deciding which kind of models are good enough to be included in the Toolbox.* (interview, ECHA)

Black-boxing, however, is not that easy, and this is visible when considering in details how the toolbox has been developed.

The development of the toolbox was conducted step by step. The latest version of the toolbox was released in December 2014, with, according to the person in charge of the toolbox at the OECD, “all kinds of new functionalities”[[3]](#footnote-3). When he mentioned these “new functionalities”, this person was referring at first to design choices making the toolbox more user-friendly. Yet the evolution of the toolbox is not only a matter of making the toolbox more user-friendly. It is significant of an iterative process inherent to the development of QSAR models. Making the toolbox even more robust means providing the toolbox with data. The more data the toolbox can process, the more robust the model is. Hence the successive versions of the toolbox rely on experimental data provided by various actors. ECHA provides data provided by the companies that register their substances; other actors such as private companies or organizations developing QSAR provide more precise date, targeting for instance particular endpoints (such as carcinogenic effects). The permanent refinement of the toolbox according to the data it is fed with is a never-ending process – and inherently so since there is an infinite variation of substances, descriptors and potential endpoints.

This requires a permanent revision of the data with which the toolbox is fed. This is undertaken by the members of the toolbox management group, which includes, among others[[4]](#footnote-4), experts from member countries regulatory authorities, and is not a straightforward process, as explained during an interview by the person in charge of the toolbox at the OECD:

*Okay so basically first – always the decision about inclusion to the Toolbox, if some database should be included or not to the Toolbox is done by the Management Group. So basically if you want to include something to the Toolbox, you need to do the proposal to the Management Board. (…) So basically you need to describe all the facts about this data, how the data was generated or collected and so on and based on that, the Project Team is trying to assess more or less the database, so see how it looks (…) and see if this data is consistent and what might be the problems in integration with the Toolbox and makes the recommendation to the Management Board. And then the Management Board takes into account the original proposal plus Project Team recommendations in deciding, “Okay if we want to include it or not”. (…) So I think currently we have like around 40 different databases included in the Toolbox.*

Thus, feeding the toolbox with new data is not only a never-ending process, it is also a long one, implying a permanent assessment of proposed dataset, and a permanent enrolment of new users who could provide more data. This latter point helps connecting the seemingly external issue of user-friendliness with the development of the content of the toolbox itself. As more and more datasets are needed in order to successfully develop the toolbox, then it is important to make the toolbox usable for more users, by for instance, proposing them to select endpoints of potential interest and providing them with relevant descriptors.

One can then grasp an important characteristic of the development of a would-be black-box such as the OECD toolbox. Such a development implies enrolling more and more users, as a way of ensuring both the collective legitimacy and the technical validity of the instrument. This enrolment process is a constitutive part of the toolbox and not a primary phase before stabilization. In other words, the toolbox cannot provide a stable public proof of its scientific validity and regulatory acceptability, but is based on the permanent re-working of the public proof.

A consequence of this (and of the fact that the toolbox is just one possible instruments among many others, such as private software, for the grouping of chemicals and the anticipation of their risks), is that no general black-boxing is possible. Within the European institution, this is formulated as such:

*The process of (Q)SAR acceptance under REACH will involve initial acceptance by industry and subsequent evaluation by the authorities, on a case-by-case basis. It is not foreseen that there will be a formal adoption process, in the same way that test methods are currently adopted in the EU and OECD. In other words, it is not foreseen that there will be an official, legally binding list of (Q)SAR methods.* (ECHA, 2008: 27)

This quote contrasts the test methods developed by the EU and the OECD and regularly used to conduct toxicity assessment. No such consensual production exists for QSAR, and this is not a matter of waiting long enough for standardization to be possible. This is inherent to QSAR itself, and implies that rather than relying on transferable black-boxes (such as the test methodologies produced by the OECD about experimental toxicity), the model-based government of risks is based on flexible instruments. Flexibility, here, relates to the process whereby public proofs are constantly re-worked. In this process, an important component is the requirement for transparency, and, as we shall see, this requirement goes hand in hand with the ambivalent black-boxing process.

Let us get back to the OECD toolbox on this latter point. Since many choices need to be made to construct and use models, then regulators might be wary of too complex instruments that they would be unable to apprehend (regarding e.g. the hypothesis, the domain of applicability, or the statistical methods being used). So the objective of producing a ready-made tool expected to be used as a black-box is ambivalent. Consequently, the delegation to the toolbox cannot work without a requirement for transparency. An ECHA official put it in the following terms during an interview:

*I think what OECD understood very quickly, (…) that the most important, most critical element for Regulators is the transparency of the model. If you have a very sophisticated statistical model (…) this is not very convincing for Regulators because they don’t exactly know what was exactly the training set which you used to train those networks and even if you see that they are performing very well on your test validation set, it doesn’t mean that they will perform equally good on the new substance which are out of the validation set. And this is the basic problem of all those advanced QSARs, that they are not so transparent because they are very complex and regulators have always this problem in understanding what will the logic behind the tool? What kind of features were driving predictions?* (interview ECHA)

The successive versions of the toolbox reflect this requirement for transparency. For instance, the newest version of the toolbox makes it possible for users to have information about the datasets:

*What we’re also going to develop in the new version is to have a kind of reliability score related to the database and the profile so that at least they are all well documented so the regulators can decide that we are very transparent on how these databases or profiles are constructed, what kind of chemicals have been used to develop – which are included in the database. So if you go to the Toolbox you also have an “about” section. You select a database and click on the “about” section then you will get information on the database.* (interview, OECD)

The concern for transparency in QSAR modeling is not limited to the OECD toolbox. In fact, the issue is even deeper in for others tools, such as software developed by private companies and used by companies in ways that are not always easily understandable by regulators assessing registration dossiers. The use of QSAR for regulation making is indeed characterized by a multiplicity of would-be black-boxes produced by public and private actors developing software, based on different statistical approaches. Although guidance documents have been produced by public bodies such as ECHA, and although attempts at producing common instruments such as the OECD toolbox have been undertaken, the situation of diversity of instruments still remains. Consequently, public agencies are in a permanent need for re-opening the black-boxes used by companies. Consider for instance how members of the French public agency for environmental safety describe their roles in assessing the use of QSAR models by companies:

*- And I think that the stake for us is to identify the limits and confront the industrialists. (…) If we are not able to deconstruct the reasoning and know what there is in black boxes, then we can’t argue with what companies propose! We can’t say that we don’t accept because we would have checked the domain of application, or whatever. That’s why we need internal competencies for that… -… for a counter-expertise really.* (interview, ANSES)

Thus, opening the black-box of models is a permanent requirement of regulators, which makes them prefer hybrid approaches combining experimental and modeled data rather than unique modeling solution based on sophisticated, black-boxed tool:

*Yes and this is something which is important for regulators because if I will know that for example the prediction is backed up by some solid hypothesis which is confirmed by for example different in vitro observations or other observations in vitro from similar substances, this is for me something much more important than just predictions generated by super duper fancy logic, for example neural networks. And another important point is really transparency. Regulators are not looking for the tool which will give you the smallest possible error in predicting something on your validation set; regulators are more keen on something which they can understand how it works and they can extrapolate it to the normal – their own experience. It’s even easier to accept the tool which gives you some error, like for example a few units plus or minus, but you know that this is really more or less what’s going on and this sounds reasonably good, rather than using some very advanced mathematical model which you cannot really follow and you don’t even know exactly how those features have been generated by the model.* (Interview, ECHA)

Thus, the regulatory use of models plays on a subtle balance between the mobilization of black-boxed tools and a call for transparency that makes regulators refrain from accepting too sophisticated models that could not be easily deconstructed. As opposed to a situation of “mechanical objectivity” in which the production of public proofs could be delegated to a black-boxed instrument, QSAR models suggest that what is at stake is the production of a “regulatory objectivity”, within which multiple conventions ensure the acceptability of the approach (cf. Cambrosio et al., 2006). In practical terms, this also means that regulators need to craft administrative procedures that would allow them to gather information about how QSAR models have been developed and used. An example of such procedures is the “QSAR model reporting format”, described as follows by Andrew Worth during an interview:

*Documenting models in a consistent way (…) doesn’t go in to the minutiae of model development and data curation and so forth, it – in a sense it describes what you get at the end of the model building process and it doesn’t describe all of the steps during the model building process and if you like the quality assurance that’s gone in to that so if you’re thinking of something like good laboratory practices for in vitro methods, that’s – it’s not just documenting what comes out of the pipeline, it’s documenting the procedure and that you know – the traceability of that procedure and the QSAR validation – it’s called the “QSAR Model Reporting Format” and it complies with the Validation Principles, really just documents what comes out at the end and it doesn’t go in to all the details of how you’ve done the model and how you check the quality of data and so forth.* (Interview, A. Worth)

This quote clearly shows that the requirement for transparency about models does not mean that all possible information about QSAR models will be provided to regulators. Rather, they attempt, at this stage again, to adapt a flexible approach allowing them to navigate the particularities of QSAR models, and their flexible domain of application.

**3. Conclusion**

In this paper, we have discussed the ways in which QSAR models propose a mode of governing anticipation based on flexibility. Using these models for the regulation of chemicals indeed implies:

* The construction of flexible categories, as the grouping of chemicals is not settled once and for all, but redrawn according to scientific and regulatory considerations embedded in the very construction of QSAR models;
* The definition of flexible validation processes, as the validation of QSAR models cannot be standardized but re-adapted for each case;
* A process of flexible black-boxing, in which the production of instruments expected to provide public proofs is permanently re-worked, and black-boxes are constantly re-opened by regulators in search for transparency.

The government of anticipation that emerges from these considerations is quite different from the public administrative of chemicals risks based on experimental toxicology. In the latter case, categories are supposed to be defined, and phases of risk assessment and risk management neatly distinguished. In the case of QSAR models, the forms of scientific validation and political agreement are quite different. Flexibility, for that matter, appears as both an epistemic and a political characteristic. We can hypothesize that it describes an emerging mode of government that could be identified on other technical domains as well.

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1. \* Both authors are at the Ecoles des Mines-ParisTech. [↑](#footnote-ref-1)
2. Sheila Jasanoff has shown that the 1983 report of the U.S. National Research Council, *Risk Assessment in the federal gouvernment : managing the process*, known as the *Red Book*, established the priority of the risk assessment/risk management boundary, while simulataneously recognizing in explicit ways that risk assessment was a value-ladden process. [↑](#footnote-ref-2)
3. Interview, OECD toolbox team [↑](#footnote-ref-3)
4. While the composition of the group remains secret, it is composed by representatives from national regulatory bodies, industries — esp.from the pharmaceutical domain — and from international institutions. [↑](#footnote-ref-4)