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Digitalizing risk assessment: the complex paths towards predictive knowledge systems for chemicals safety

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Introduction

With the data deluge and rapid development of new IT systems to apply machine learning algorithms, science seems to be pushing the limits of risk assessment, and promises a heightened capacity to predict perturbations and hazardous patterns in complex systems. This short paper aims to gather lessons from the study of the development of computational tools for chemical risk assessment, to understand how computing innovations unfold, and which technological promises are actually fulfilled in matters of prediction. This is done in the spirit of addressing the questions laid out in the workshop invitation, notably “what, of all this, is realistic and unrealistic?”

The paper engages with such questions as: How far can we regulate sociotechnical systems thanks to continually produced and modelled data, as claimed by specialists of computational or data sciences? How do we get to realize what is even possible and credible in new predictive practices? How and to what extent does this realization alter the development of databases, algorithms and other modeling tools applying in risk management systems?

I will discuss the development and use of computational tools for the safety of chemicals from the perspective of the sociology of science and technology and regulation research. Overall, the perspective here is that of data and algorithms as knowledge systems that inform regulatory action in the area of risk and safety.

In the remainder of the paper, I first outline what risk assessment is. I then touch on the digitalization of risk assessment: the rise of new computational tools and practices in this area of hybrid practice spanning predictive science and risk management. The third part is more empirical: it outlines the history of the development of tools for predicting chemical safety. The concluding part discusses the empirics and puts forward points for collective discussion, that broadly concern the path of development of digital knowledge systems and expectations that can be formulated as concern artificial-intelligence, ‘big data’-based predictions.

Risk assessment and risk regulation

A number of technologies are regulated because of the possible hazards that they represent for their users and for the public. From aircrafts to chemicals plants, through food ingredients and chemicals, most of the technologies that are recognized as potentially hazardous are submitted to some form of risk assessment. Over time, risk assessment has indeed become a normal regulatory instrument. Risk assessment is an element of risk regulation regimes, namely its “informational” part (Hood et al. 2001). It is comprised of dedicated techniques and routine processes, through which the conditions of appearance of hazards may be determined (their frequency, most likely localization...), and corresponding regulatory controls legitimately decided.

Risk assessment means anticipating or predicting hazardous outcomes, without having necessarily experienced or observed those. It is the product of extrapolations. These extrapolations require making multiple assumptions, to fill in data gaps. These assumptions may differ from one risk assessor to another. Risk assessment may be performed in a close environment, within the bounds of a community of people who think alike and share assumptions. But, as a matter of regulatory action and public concern, risk assessment is seldom performed in such a context. And it may give rise to public controversies or disputes. It is almost always necessarily political: we're in the area of trans-, post-normal or regulatory science. These terms, in various ways, characterize the tensions that are inherent in these scientific exercises that take uncertainties as their object. It is a process marked by interpretative work and flexibility, and by frequent controversy among the people involved.

Risk assessment may be more or less “reductive”: it may focus on what is known, in risk research or risk sciences, as the “agent”. In this case, risk assessment consists in testing this agent in experimental environments, to determine generic properties and effects. In this case, risk assessment follows from the consensual identification of what Hilgartner has called a “risk object” (Hilgartner 1992): a technological element to which a number of potential hazardous effects are consensually attributed. Risk assessment, however, may be more systemic, in this that it rests on the assumption that risks are diffuse consequences of the functioning of more complex systems involving various agents and effects, with no possibility to isolate one, supposedly more meaningful or concerning linear agent-and-effect relationship. This tension underpinning risk assessment may be illustrated by the debates pitting chemists and toxicologists on the one hand (who see the chemical substance as the cause of the risk, and develop apparatuses to know the properties of this substance) and ecologists and ecotoxicologists on the other hand – who think in terms of systems, in which substances circulate and produce multiple intertwined effects, that may not easily be disentangled.

There are other key dimensions to risk assessment. This risk assessment takes several forms. It can be ex-ante: it applies to the development of the technology in question, and informs the decisions to put it on the market or in use more generally. It may take place alongside the use of the technology in question. It is then called monitoring, surveillance or vigilance. Risk assessment may be performed directly by regulatory authorities, but is as often delegated to the organization that is being regulated, or done collaboratively by the former and the latter. In this case, risk assessment needs standards, templates, certified tools, the use of which may be required from the regulated organization, to make sure risks are properly controlled, or that the risk information produced is reliable. Regulatory bodies in turn may check the information that is delivered by the regulated organization, and control risk at a distance (informational regulation). We're talking about a process that, even though it is a part of a regulatory regime, is a joint process involving industrial actors and knowledge as much as the actors of administrations, and of the scientists that are coopted in it (and as such are quasi-public actors; they have some of their responsibilities and must heed the expectations towards governmental bodies, such as transparency and neutrality). Because risk assessment is a joint effort involving the sharing of knowledge and information, the various actors and interests involved need to agree on a definition of what is at risk, that will be the target of the knowledge effort – a particular object or agent, or a more open and diffuse system.

Computing risks

Risk assessment is a process that has always made massive use of science, and particularly of modeling. Modelling is a process that consists in formulating series of equations to capture the functioning of a system, and informing the parameters of the equations with various measurements and data, in such a way that various states of the system may be simulated.

Modelling allows extrapolating from the data points available (of which there may be a relative paucity), to other situations, scales and time-periods.

As concern chemicals, modeling has always been necessary. Chemicals cannot or must not be tested directly in the human body, in the environment or in the industrial conditions in which they will be used, but are on the contrary tested in experimental, simplified conditions. The toxicity of the chemical is tested on animals (and toxicologists and chemists speak, tellingly, of the various “animal models” (i.e. species) that can be used to perform these experiments) or in vitro. In this sense, risk assessment is a model-based science, if we understand models as a simplified, scale-reduced analog, or representation, of a system.

When one talks about the digitalization of risk assessment, one essentially refers to the rise of what has come to be known as computational sciences in this area (as concern chemicals: “computational chemistry” or “computational toxicology”). With computational sciences, what is appearing is not modeling or the ambition to predict: these are the very epistemic foundations of risk research. The computational turn rather marks the rise of:

- first, the ambition to work with mathematical or statistical models, more so than physical or biological analogs. Computation refers to, essentially, calculation, hence to the notion that systems can be captured through sets of equations, constituting a mathematical model that are representative enough to be used to predict with some accuracy. When it comes to chemical risks, this is best articulated by Melvin Andersen, who emerged as one of the leaders of the field of computational chemistry and toxicology over the past decades (Andersen 2016): rather than manipulating substances and animals, he enjoys working with equations and numbers: *“I enjoyed this process of modeling, of being able... Modeling things. Writing equations for them and see whether what I was seeing in my head is right. That is the process.”* To be sure, statistical modeling has always been necessary in risk assessment, even when physical experiments or tests were at its heart (i.e., analysis of the data points generated by the experiment). But the difference here is that computational scientists decouple statistical analysis from the conduct of experiments. At heart, they believe that more reliable predictions may be made from the set same of existing data, than would be the case without application of these mathematical models.
- second, the material capacity to produce more data, and more varied data thanks to the diffusion of sensors and other data-generating devices across the environment. There is a material, infrastructural aspect to computational sciences, which is the fact that more aspects of sociotechnical systems get digitized in this sense. When it comes to chemicals, this means that not only are there databases about the properties of a substance (its stability, flammability, solubility, and so on: what chemists call “phys-chem” properties), but also its effects in animals, at various levels and time-scales, and perhaps various effects in broader, human populations too. One of the major developments concerning computational sciences when it comes to chemicals, is the production of so-called “biomonitoring data”, concerning various biological and pathological trends in human populations. These data derive from efforts in epidemiology and so-called exposure science. They allow capturing potential effects at a broader scale, in systems that are not amenable to physical testing. Another major development consists in the multiplication of detectors in various environments, allowing to capture the presence and quantities of chemicals in various environments.

- third, the automation of such data generation systems, and their continuous analysis by supercomputers or what one may call “predictive machines” (Benbouzid and Cardon 2018). Systems oriented towards big data and machine learning, specifically, are underpinned by an imaginary of continuous, non-human-mediated production of data that can directly feed stable, previously-trained algorithms (e.g. neural networks), that will then turn out predictions as data come in.
- fourth, a concomitant expansion of a system-based perspective in a number of disciplines: the theoretical understanding that most phenomena in life can be explained as effects that are emergent from complex systems. The computational turn is intimately related to the redefinition and revamping of many disciplines (geography, sociology, biology...) as complex system sciences, emulating physical sciences (Li Vigni 2020). This is not entirely new of course: the systems perspective was integral to the rise of cybernetics, for instance¹. But as the perspective is wedded to more intensive, more voluminous, rapid data-production systems, prediction becomes both much more complex, and still appealing. Liu, one of the scholars that worked to define systems biology, writes that “there is a common understanding that this discipline seeks to explain biologic phenomenon, not on a gene-by-gene basis, but through the net interactions of all cellular and biochemical components within a cell or organism. Operationally, systems biology requires the ability to digitalize biological output so that it can be computed, the computational power to analyze comprehensive and massive datasets, and the capacity to integrate heterogeneous data into a usable knowledge format. Thus, systems biology can be described as “integrative biology” with the ultimate goal of being able to predict de novo biological outcomes given the list of the components involved.” (Liu 2005). The sort of prediction that systems-oriented, data sciences are interested in, are predictions that derive from the full comprehension of the functioning of a system, yet can be focused on the evolution of elements of the system.
- fifth, digitalization refers, as concern risk assessment and risk regulation, to the use of digital twins, or what one may call integrated simulations of complex systems. Aviation regulators on either side of the Atlantic base their decisions to approve the design of an aircraft, on digital simulations more than on experimental flights (even though statistics computed out of hours of flight experience count a great deal in achieving reliability)(Downer 2017). Technologies allowing to create highly representative ‘digital twins’ have massively advanced. These twins are considerable credible enough for regulators to trust them. Pharmaceutical companies nowadays adopt comparable technologies of simulation than airline companies have used for decades. Simulation software companies such as Dassault System have massively invested in the area of life-sciences, defending the view that simulation technologies can be equally useful for simulating and predicting biological systems. The Biovia software series allow 3D modeling of chemicals and assemblage of data from heterogeneous knowledge systems around the model of the chemical. Currently, the trust that DS places in the

¹ One of the leaders of the field of systems biology, Hiroaki Kitano, opened one of his paradigmatic paper published in Science, by a reference to Wiener (“Since the days of Norbert Wiener, system-level understanding has been a recurrent theme in biological science”)(Kitano).

representativeness of their simulations is high, leading them to engage in efforts to persuade regulators to accept simulations as evidence of regulatory conformity. Likewise, the pre-marketing examination of pharmaceutical products involve at greater doses, the consideration of simulations, notably as concern the extent and effect of impurities. It has become mandatory to provide elements drawn from models, about these impurities.

Taken together, the computational turn in risk assessment (here, of chemicals) can be broadly characterized as the move towards the continuous modelling of large sets of data documenting processes at various scales of a system, to simulate and regulate the latter. The following image captures this epistemic aim as concern biological sciences. It gives a good sense of what is the truly novel aspect of computational sciences and techniques of the past decade or so: a sort of integrated form of simulation, where one aims to describe and predict a greater number of aspects of a system, at a fine-grained level (Ruphy 2014).

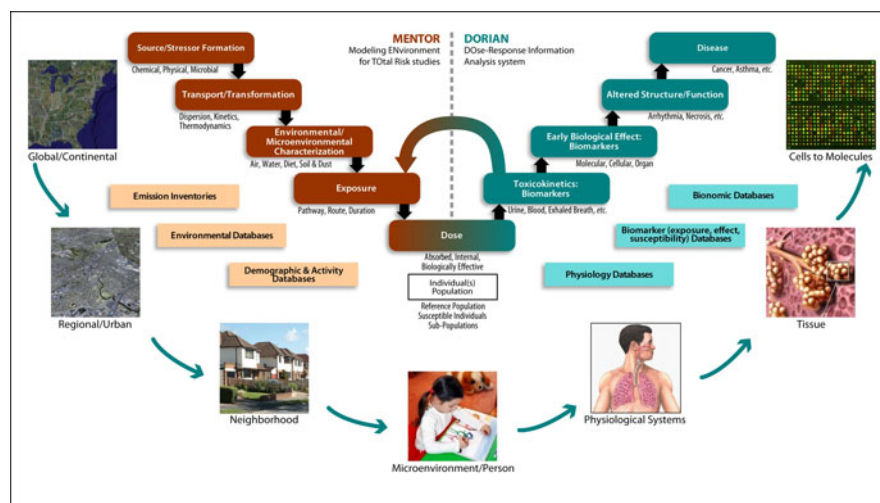


Figure 1. Representation the environment/biology nexus as a complex system to be analyzed at multiple scales

Computing chemical risks: the historical development of tools and practices

It is important to note that this is an area that is full of “technological promises” and epistemic ambitions, that may not all be fulfilled, or not in this form. A certain version of these practices and tools of prediction are likely to become reality, not necessarily the ones that are put forward by roadmap champions and other disciplinary visionaries. Looking back at what has been developed in the field help appreciate the path of technological development and epistemic change through which current applications have taken shape. When it comes to chemicals and their risk assessment, three predictive techniques have been developed since the 1970s.

Historically, the first predictive, computational tool that was developed was one that aimed to characterize the properties of molecules through systematic analysis of the relationships between their structure, and their biological effects – the so-called structure-activity relationships (SARs)(Boullier et al. 2019). A quantitative SAR is a statistical analysis (by regression or classification or else) of the biological activity of a group of two or more chemicals that have some structural similarity, as captured through a chosen descriptor of the chemical. The modelling of causal relations between chemical properties and biological impacts is rooted in fundamental chemistry. The quantitative approach towards these correlations was pioneered by a Professor of Chemistry at Pomona College in California,

Corwin Hansch, now known as “father” of computer-assisted molecule design. It rests on the conduct of multiple strictly standardized experiments on molecules with the same kind of structure (co-generic molecules). Once a sufficiently powerful set of data has been produced, a statistical analysis can be run, to try and capture the correlations between structural properties and the biological effects. The resulting correlations can then be used to formulate a mathematical equation – a model – that may be used to predict the effects of a molecules without physically testing these. The challenges that QSAR research is facing typically concern the generation of sufficiently large sets of comparable data across a whole class of chemicals (a highly intensive endeavor), and the availability of both training sets and alternative data sets to validate the models once formulated. Without such data, modellers end up producing an over-fitted or under-fitted model, that decision-makers will hesitate resorting to (Thoreau and Laurent 2019). Connecting model development to larger sets of data made available by pharmaceutical companies is one of the key hopes here for the future development of the field.

Another technique has been developed in the space of chemicals risk assessment, aimed at modeling so-called dose-response relationships in biological organisms, better than an animal test can achieve. The technique is known as PBPK, for physiologically-based pharmacokinetics. PBPK modeling consists in simplified descriptions of the physiological system exposed to a chemical substance. By modeling the organism and the biological mechanisms involved in the metabolism of the substance, one can compute the dose at which the substance will produce hazardous effects in the organism. Models represent relevant organs or tissues as compartments, linked by various flows (notably blood flows) in mathematical terms. The parameters are calibrated with data emerging from animal experiments or clinical observations. PBPK modeling really started in the 1970s, once sufficient data and computer tools became available to establish the doses at which anti-cancer medicines could be delivered to various organs. The application of PBPK to industrial chemicals started at the beginning of the 1980s, to define so-called reference doses for chemicals: the levels of concentration at which they can safely be considered to not cause harm. This could be done because of the accumulation of data about volatile chemicals (then under threat of regulatory restrictions): data about how much people inhaled chemicals, data about biological metabolization of these chemicals, and data about how much chemicals were eliminated by the human body and exhaled. These data originated, notably, from the use of costly inhalation chambers. Once databases were elaborated, models started to be elaborated and calibrated in more reliable ways, for more chemicals, allowing to envisage the possibility to model together the chemical and the human body. In this field, the main challenge has always been the capacity to calibrate the model with realistic and varied biological data, to counterbalance the drive to make predictions based on more quickly-produced, but less representative and relevant, average values (Demortain 2021).

A third technique consists in developing what is called biologically-based mechanistic models, to analyze the functioning of the human body and biological pathways inside those, as well as their interactions with substances. The resulting “biologically-based dose response” (BBDR) models pursue the same kind of aim as PBPK – doing better than animal tests in terms of prediction of risk thresholds. Indeed, some of its champions are the same than for PBPK (Andersen et al. 1992), and BBDR was also developed to counter or moderate regulatory drives on critical chemicals such as dioxin (Demortain 2020). Instead of capturing biology through equations, as PBPK does, it banks on rapidly evolving knowledge of the cellular pathways through which chemical substances trigger potential toxicological issues. These theoretical models of biological organisms are supposed to guide the interpretation of empirical toxicological data. Much like PBPK, the reliability of this sort of modelling is

limited by the data that are being modelled, and their capacity to represent “inter- and intraindividual heterogeneity” (Crump et al. 2010).

All of the above techniques, as briefly mentioned, have been limited by the slow and costly generation of data through in vivo or in vitro tests, as well as by the quality of the hypotheses that guide their interpretation. While modellers often resort to short-cutting claims such as the one that they can predict risks thanks to better maths and bioinformatics, the truth is that models do not exist without experiments — or more generally from an infrastructure for generating standard, curated data — and from human interpretative work, and the necessary biological knowledge to perform it. Often times, in practice, modelling is a tool that mixes with experiment and biological theory, but can not hope to replace them.

In terms of toxicity data, the game-changer has come from the genomics (and the corresponding *toxicogenomics*) revolution, namely from tools allowing to generate massive sets of data points about genetic events out of one single experiment, and at high speed. “Omic” techniques, such as micro-arrays, allow to represent all of the events in a biological system associated with the presence of a chemical substance. Robots allow running multiple assays on dozens or hundreds of substances day after day, generating massive sets of data, to be modelled by biologists. This toxicogenomic effort emerged a little after 2000s, after the three others introduced in this paper.

Under the impetus of the chief of the US National Toxicology Program, Chris Portier (a biostatistician who had, among other things, worked in the area of PBPK and BBDR), a draft of strategy was elaborated around 2003 « *to move toxicology to a predominantly predictive science focused upon a broad inclusion of target-specific, mechanism-based, biological observations* ». The Environmental Protection Agency embarked on a similar effort a few years later. Teaming up, these institutions soon developed a vast, multi-institutional multi-annual effort known as Tox21, to conduct hundreds of assays on thousands of substances, thanks to high-throughput technologies. The central character in this program, which took off in 2008, is a robot from the swiss company Stäubli, of the sort that one generally encounters in industrial plants. The robot is programmed to be able to manipulate plates containing dozens of mini-petri-dishes, in which different dosages of multiple chemicals are injected, day after day, and multiple assays conducted.



Figure 2. Source : NTP, 2017, Tox21: Chemical testing in the 21st century.

The result is an immense set of data, in which toxic patterns of biological systems can be detected. This is done, notably, through open data challenges: the Tox21 institutions have called for teams of computational biologists around the world to search through their data to generate such models. This is where machine learning, and “new” IA methods — renovated IA methods rather, since the algorithms used were known — come in²: models are being constructed from the ground up, through supervised exploration of the mass of data to identify (or learn) patterns.

- At about the same time as the Tox21 effort took off, a panel of top toxicologists and specialists of the field of toxicity testing, led by Melvin Andersen, had rationalized these multiple developments. The addition of high-throughput toxicogenomic to previous developments allowed to envision a future in which data would be available for many possibly toxicity pathways concerning multiple substances, to radically change how the toxicity of chemical substances would be tested: not as an isolated object with defined properties (such as a toxicity threshold), but as elements of a biological system acting at low doses, through multiple pathways. In other words, a knowledge system that would be representative of the reality of how biological systems function in the current chemicalized environment.
- The resulting “vision” was published by a branch of the US National Academies (the National Research Council), and heralded as the right guiding vision. Interestingly, the vision seems to cap all previous efforts in the area of model-based, predictive toxicology: efforts in QSAR (to characterize properties of a substance), PBPK and BBDR (to formulate mathematical/biological models of the organism) and in high-throughput in vitro testing, were now the building blocks of a knowledge system allowing to “*evaluate relevant perturbations in key toxicity pathways*” (NRC 2007, p.7), as opposed to simply measure the levels at which an object, taken in isolation, may prove harmful.

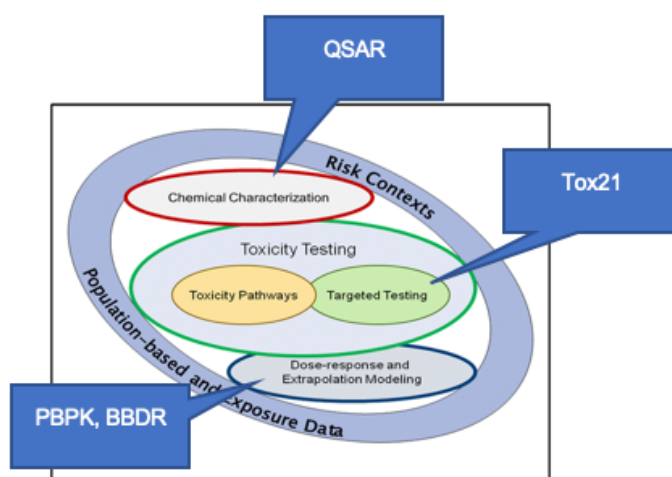


Figure 3. Adapted from NRC 2007

² “The Tox21 Data Challenge provides the unique opportunity to compare the predictive abilities of different computational methods for biological activity, specifically, those related to toxicity. The Challenge participants employed a wide range of chemical descriptors and/or fingerprints for small molecule representation, and machine learning algorithms for modeling. Models employing the deep learning algorithm showed the best predictive performance. (...) Other articles described models that employed classic machine learning algorithms, such as Random Forest, Support Vector Machine (SVM), k Nearest Neighbor (kNN), and Naïve Bayes (Drwal et al.), with different combinations of molecular descriptors, each with their own spin on the specific implementation of these methods for model construction.” (Huang and Xia 2017).

Conclusion

This concluding section puts forward a few points for discussion, revolving around the issue of the evolution of data sciences and systems to tackle risks. The following remarks are made in the hope of being able to compare across areas of safety management, beyond chemical risk assessment.

A first observation concerns the intertwinement of modeling and simulation with generation of data through experiments and field observations. This is something that the sociology and history of science have long emphasized (e.g. Morgan 1999). However, the current development of IA rests on a discourse about the all-powerful machine learning methods, and their unabridged capacity to learn from data, thanks to powerful computers. However, as can be gathered from the brief descriptions above, the various families of modelling techniques have been restricted by the same problem: the availability and the diversity (or representativeness) of the data that are being modelled. A simple conclusion to draw from this is that artificial intelligence will represent an innovation and a new leap in modelling capacities, in so far as it is matched by the parallel deployment of larger infrastructures of data.

A second observation derives from the allusion above to the development of digital knowledge systems through cross-area diffusion of tools. Some historians of science and technology have noted that numerical modeling and simulation is a lingua franca in sciences; a form of generic technology that produces comparable epistemic effects across disciplines (Lenhard et al. 2007). Artificial intelligence and big data are no exception, judging by the existence of families of algorithms, for instance those that are now placed in the category of deep learning, that are put to use in various areas. In the present case, one sees the application of deep learning late in the process, in the context of the Tox21 program. One also sees the importation of a robotic technology from industrial fields. But all other knowledge systems are concerned by this cross-area development of simulation techniques. To give one further example: PBPK modeling has developed and gained credibility thanks to the use of generic programming languages (e.g. Fortran), allowing more people to engage in this area, generate more models, creating an emulation/comparison of models, resulting in the improvement of the technique altogether. One key question derives from the transversal nature of innovation in digital knowledge systems: the borrowing of tools and techniques from other areas quite clearly participate in the drive towards more simulation in areas that were hitherto less concerned by it, and that will conflict with the area-specific possibility to develop credible models which is, as noted above, dependent on the existence of large and varied sets of data about the particular thing that is being modelled in this area. Accessibility and representativeness of data may not be equal to what it is in other areas. And so the promise of prediction that comes on the back of imported tools and techniques, may be conflicting with local conditions of realization of that promise.

A third observation concerns what I have called above “risk objects”, or what STS also calls “epistemic objects” (Knorr-Cetina 1999). As can be gathered from the brief description above, various risk/epistemic objects are construed by the various predictive, data systems that have been put in place over time. QSAR looks at the properties of molecules, and models classes of chemicals. PBPK looks at the dose of chemicals in the human body, and models physiological systems. In the HTP toxicity testing system of Tox21, it is the biological pathway that is the object of the system. All of these objects are worthy of data production and modelling, and are seen as proxies of broader systems. But they are heterogeneous objects, and the systems that are in place to know these objects are distinct, and not

necessarily compatible. They may be, quite simply, the incarnation of different ways of modeling or predicting (Aykut, Demortain and Benbouzid 2019). In the case of Tox21, even though a holistic vision has emerged, eventually, there is no assurance that these knowledge systems can be further integrated, or that the current development of artificial intelligence will bring coherence to past developments. It is so because there is “ontological politics” involved: a search, that may be contentious, for a realistic definition of what the problem is. A risk can be defined reductive ways, assigned to an object that is deemed easier to regulate and control (i.e. the molecule). Or a risk can be defined in a more diffused, systemic manner, and lead to the exploration of chains of causation between objects forming a complex system.

Third, the more one evolves towards knowledge-systems-for-systems as it were (in other words, the more knowledge systems are developed to model complex systems, as new data are made available and learning algorithms are re-developed), the more complex it becomes to intervene in and regulate these systems, since modeling will reveal complex chains of causation and an intertwining of causes. In the present historical case, this is illustrated by the fact that, as knowledge systems accumulate and evolve towards greater complexity, the ontology of the “dose”, “threshold” and of the risky object – the chemical substance to which a risk can be attributed – loses ground. This raises the issue of how decision criteria are forged in the space of knowledge systems that are designed to turn out complex correlations, rather than to isolate linear causation chains between an agent and an effect. This implies that big data systems may be of greater value for actors that are in active, operational positions, serving as a form of monitoring device, rather than as a one-off advisory mechanism controlled by scientists that would be external to management. In short, a digitalized risk assessment will affect the normal relationship, and expected separation of, risk assessment and risk management.

Algorithms are not by nature un-transparent. But there may well be a gap between their mode of development, and the level of trust and credibility that is demanded in certain areas of use of algorithms. That gap is more or less wide, depending on the ways in which trust can be generated alongside the development of these tools; that is, depending on how far they are validated and audited. And so, one of the critical issues as concern digitalization of risk assessment is the ways, speed and modes in which algorithmic methods can be audited while being developed. While the demands of representativeness and trust will be higher, the mode of development of data instruments make them potentially less trustable than others. They remain under test for long periods of time, and are incrementally developed. They are developed by private, commercial firms. The question is how and to what extent these developers are embedded in a set of relationships with potentially critical specialists of these knowledge systems, who care to check their validity, reliability and transparency for public purposes and try to weigh on the choice of developers.

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