Chemists' Responsibility for the Health Impacts of Chemicals: Green Chemistry and Its Relation to Toxicology

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Abstract: Green chemistry was developed as a revolutionary change in the ethics of the discipline: chemistry was assuming its responsibility for environmental and health hazards, and proposed to become one of the main actors in preventing them. Scientists became morally obligated to make a concerted effort to reduce the toxicity of new molecules and processes. Using historical insights and analyses of current research in the United States and France, I address the relationships between green chemistry and toxicology in order to address the question: are chemists living up to the early ethical promise of green chemistry? Twenty years after the birth of this movement, and despite the availability of conceptual and methodological tools, it has proven difficult to integrate concerns about toxicity into green chemistry. I argue that the reason why some green chemists have taken limited moral responsibility for chemical risks, is related mainly to: (1) a feeling of weak empowerment in the chain connecting innovators, producers, users and regulators of chemicals, and (2) the regulatory and academic divide that has been historically institutionalized between chemistry and toxicology.

Keywords: *Green chemistry, descriptive ethics, responsibility, chemical risk, toxicology*.

1. Introduction: The Ethical Dimension of Green Chemistry

"As a chemist puts pencil to paper to design a new chemical synthesis, he or she is making intrinsic decisions: decisions about whether hazardous substances will be used, whether hazardous materials will have to be handled by workers, whether hazardous wastes or by-products will require special disposal, and the like." (Anastas & Warner 1998, p. 10) This is how the founders of green chemistry (GC), Paul Anastas and John Warner,[1] described in the

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1990s the ethical responsibility of chemists – assumed unconsciously in the daily routine of their laboratories – regarding the impacts of their work on the health of potentially millions of workers and consumers.

Synthetic chemists did not traditionally consider themselves as actors capable of influencing environmental impacts. The great upheaval of GC, in the context set by its founders, concerned the status of the chemist-researcher in the chain between laboratory, industry, consumer, and politics. Chemistry recognized and even claimed its socio-economic role, and declared itself in a new consciousness. Since it is lab chemists who invented substances and processes that have environmental and health impacts, they also had the power to influence this pollution by including it early on in their thinking, when new molecular structures and their uses are designed. Laboratory research can lead to innovation and thus commercialized products, so it would also have the capacity to integrate upstream any concern for the health and environmental effects of chemistry. This new power claimed for chemists would inevitably be accompanied by a new moral, societal responsibility; this translated into an ethical requirement to consider the health effects of chemicals, not as a marginal or nonexistent aspect of their work, but as the primary aspect, integral to planning research. This was a procedural rather than substantive ethical standard. What mattered was that chemists would *organize their work so as to best understand and limit the toxicity of its outcomes*.

In one of the first books about GC, Anastas and Farris (1994) briefly mentioned the term 'green chemistry' in the introduction, and focused arguments around the concept of 'benign by design'. The first chapter highlighted the new role of the chemist. While conventional chemistry did not consider itself an actor in environmental chemistry, it was now at the heart of pollution prevention (Anastas 1994). Thus, pollution would no longer be merely the subject of research for a marginal community in chemistry, such as analytical and atmospheric chemistry, but rather a question that concerned the very nature of its noblest branches and the most representative of the discipline, which are those interested in synthesis. 'Benign by design' greatly altered the work of chemists who were historically interested in two aspects: first, the functions that substances can perform in a useful way, and, second, the industrial production costs of those substances. GC added a third criterion, namely effects on health and the environment that must also be considered at the stage of designing molecules. This change triggered other cascading changes in the most elementary principles that guide the work of chemists.

Thus, an important criterion for 'classical' chemists is the price of raw materials. More importantly, the yield of a reaction is a key measure of the scientific and economic interest of a chemical transformation. The yield is the percentage of product obtained with respect to the theoretical amount that can be derived from a certain amount of reactant. Scientifically, yield is a good indicator of the thermodynamic advantages of a process under industrial production conditions. Economically, it measures efficiency of the use of raw materials. For Anastas (1994), this indicator is an insufficient measure of the performance of a reaction, especially from an economic standpoint. Since the output ignores the cost associated with pollution prevention equipment and waste treatment, it should be complemented by specific indicators for those objectives. In that regard, the Anastas chapter contained principles that should complement the classical indicators of chemistry, *i.e.* a draft of the 12 principles that he went on to publish with John Warner in 1998. These described the use of computer-assisted predictive methods to anticipate the pathways of synthesis and their potential impact, identify alternatives to toxic solvents, use alternative raw materials, and identify alternative catalysts.

In that work the elegance of a reaction, so dear to chemists, was discussed in the light of new priorities, so that the beauty of synthesis now included references to efficiency, economic viability, and environmental impacts. When Anastas revised the definition of economic calculation for a chemical process to include the costs of controlling pollution and waste treatment, he proposed a real socio-economic revolution. Traditional chemistry and its measures are inextricably linked to the classical economy and its reckless ignoring of environmental impacts. For chemistry, this recklessness begins at the level of the chemist's laboratory, via measures of indicators with no a-priori value-laden, but that resonate at the much greater level of the industrial transposition of research. Due to the effect of scale, such apparently theoretical, objective, and small-scale indicators can induce environmental and health impacts that are sometimes massive. Proposing new indicators of a reaction's economic performance amounts to proposing a new vision of the relationship between the economy and the environment. This is not a minor change. The entanglement of chemistry in the industrial fabric of modern societies means that any changes to chemistry can affect broad-scale changes in entire economic systems.

Yet the proposed change, although targeted at scientists, was also majorly political. While most existing regulations were still focused on controlling the impacts of substances at the level of risks, *i.e.*, the relationship between exposure and inherent toxicity, GC altered that perspective by putting the spotlight on the intrinsic toxicity of substances. This shift in framing inevitably transformed the sharing of responsibility for the negative effects of chemicals. In the chain between laboratory, industry, consumer, and policy, the concept of GC returns part of the responsibility to chemists, while regulation (focused on risk reduction through exposure reduction) placed responsibility squarely on manufacturers, regulators, and even consumers. GC thus became the chemists' oath of Hippocrates: above all, do no harm.

Another new aspect was going beyond the chemical industry's classical discourse of downplaying risk (*i.e.*, arguing that the risks of chemicals are low and acceptable or even non-existent compared to their benefits for modern life), to fully assume the existence and importance of chemical risk. This risk became the driving force of new research in chemistry. Chemists became aware of the decision-making power that makes their skills useful and important for controlling this risk, which can complement the political regulation that happens upstream. With this proposal, some of the founders of GC bet that the voluntary approach via educating chemists will be much more effective than coercion and guilt.[2] According to Anastas and Zimmerman (2016a), chemists cannot plead ignorance anymore to the consequences of their science, and they have the greatest influence and responsibility of all as molecular designers.

From its origins in the United States, the concept of GC spread worldwide. Its success was reinforced by chemists' perception that their discipline was in 'crisis', due to profound criticism of chemistry's role in the most vital sectors of the economy such as agriculture (*e.g.*, pesticides) and the consumer sector (*e.g.*, controversies over the role of chemicals in daily products, especially emerging concerns about endocrine disrupters). In Europe, and more particularly in France, I show below that its meanings were drafted with significant delay (10 years) and in accordance with chemists' existing concerns.

2. The Negative Image of Chemistry: French Chemists Worried About Their Social Reputation

In France, GC was seeded in a terrain already sensitive to social concern. In the chemists' community, the relationship between their science and society was, and to some extent still is, directly related to the so-called 'negative image of chemistry'.[3] However, the solutions envisioned to resolve this unfavorable situation were not the same for all chemists. Three overlapping alternatives can be easily identified, depending on how responsibility for the situation is attributed.

The first view attributes the negative image of chemistry to insufficient scientific understanding of the sociopolitical phenomena at stake, and proposes a collaboration between the human and social sciences and chemists. Understanding the controversies around chemical hazards to the environment and health would enable the identification of potential responses that are available to the chemists' research community. A second view places responsibility on the public and on the press. For chemists with that perspective, better and even more aggressive communication by their community would restore their good image. The third alternative, GC, proposes that chemists themselves should change their practices in order to alter their image in society.

The first position characterizes one of the interdisciplinary works devoted to chemistry-society relations, published right when the concept of GC emerged in the United States. This book (Bram *et al.* 1995) resulted from a symposium organized by chemists and social scientists; it starts by stating the need for understanding the societal stakes of chemistry:

> Sociologists, economists, anthropologists and historians have indeed privileged the study of the physical sciences as a model of exact science and the study of biology as an experimental science. The scarcity of research on chemistry could constitute an indicator of its status in the social body: a scientific and technical production whose specificity is ignored despite its omnipresence in everyday life and its central role in the productive system. [Bram *et al*. 1995, p. 11]

The term 'green chemistry' does not appear in the book. The question of risk is approached in view of its treatment in the laboratory, its perception by the chemists who face it in their daily work (Tatéossian & Desjeux 1995), its treatment in the media (This 1995), or its influence on the public perception of chemistry (Armand 1995). The book discusses environmental concerns in a section on 'Chemistry, Risk and Society' that incorporates both environmental science (the state of the art in environmental chemistry) and social science perspectives (analysis of policies for managing the risks of industrial accidents).

Whereas some reference is made to the need for chemistry to become closer to environmental sciences, the idea that chemists' training should change to integrate environmental knowledge was not stated explicitly like it was in the United States. Yet it clearly depicted the major role that chemistry should play in meeting the challenges posed by chemical risks: "A common feeling shared by chemists is that our developed society has linked its destiny to chemistry and that we will really fight the disadvantages of chemistry only with better chemistry "(Fuchs, 1995, pp. 261). The idea of a necessary change in the minds of chemists is beginning to emerge. Alain Fuchs[4] emphasized the irreducible socio-political dimension of chemical risks and the need to integrate that into any reflection on the place of science, including chemistry, in society. This reflection can lead to changes in the practice of the science itself:

> These debates have helped to better situate the future interdisciplinary research on chemical risks. The point is less to construct a general and unified discourse on society for facing scientific and technological risks, and more about starting from the analysis of the structures and practices from which problems arise. It is, once again, a better knowledge of the chemistry that is

> needed: we do not know much, for example, of the internal contradictions of a discipline subject to both the constraints of disciplinary logic, productive processes and a 'social demand' that is not really defined [Fuchs, 1995, pp. 262].

The second posture that French academic chemists take, regarding the relations between chemistry and society, is advocating for improved communication strategies. Their view is experiencing a reversal in the 2010s: better communication should be able to change the negative image of chemistry, without accounting for socio-political or economic phenomena. They argue that chemists should be more active at highlighting the benefits of chemistry in everyday life, which could counterbalance the criticisms against chemistry. In that vein, the CNRS 2010 gold medalist Gérard Ferey said:

> At the moment, we chemists, my friends, often feel that we are this stranger, too often and unjustly targeted by the suspicion and misunderstanding of our fellow citizens, who feel that – by forcing the line – we are that mangy, scurvy source of all evil, to use the expression of our good La Fontaine, while confusedly knowing that, like the village baker, we are indispensable. In public opinion, the image of our discipline is very bad, whether it is the chemical industry, one of the most badly felt in Europe, or the chemical products themselves.
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> In order to prepare the retort, first it may be necessary to quickly analyze the reasons for the current state of affairs and the degradation of our image in the public eye. Many are foreign to us. The very strong criticisms from a sometimes ill-thought ecology, more inclined to the ideal than to pragmatism, are one of them. The erroneous assertions of some who are more concerned with promoting their books and cultivating fear than with relevant information, are another. Finally, their communication by a press more eager for spectacular declarations than for scientific moderation have worsened the situation.
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> […] Now, that's enough!
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> I no longer want to see, and you no longer want to see, chemistry associated only with factory chimney fumes that are considered harmful; I no longer want to see, and you no longer want to see, the press making peremptory headlines out of information that is only questionable hypotheses from some of our colleagues […] Do not buy bottles of water anymore, my friends! They generate cancer […]
>
> That's enough !
>
> But, if you want it to stop, IT ALL DEPENDS ON YOU! We must, EVERYONE, through COORDINATED action, change the public opinion of chemistry and restore its TRUE PLACE. […] We must change the image of chemistry in the minds of the French public with continuous, forceful actions that innervate the whole territory, from schools to universities, from exhibitions to conferences of general interest. […] It is necessary to hammer that chemistry is essential for the future of the planet." [Ferey 2009][5]

Finally, since 2007 and inspired by those in the United States, some chemists have instead begun to talk about the relations between chemistry and society from the angle of a necessary adaptation of research and innovation practices in chemistry to social demand. This perspective characterized the interdisciplinary program of research 'Chemistry for sustainable development' (coordinated by the CNRS director of research Isabelle Rico-Lattes), which proposed to "raise awareness among researchers about the concept of eco-compatible chemistry and orient CNRS laboratories towards research in sustainable chemistry".[6] The title of this funding program demonstrates particular attention to the potential defensive reaction of the chemistry community to the 'sustainability' terminology. Chemistry 'for' sustainable development could refer to a chemistry whose research model does not change to incorporate concerns about chemical risks. Chemistry might simply need to meet new challenges, linked in particular to pollution, but without necessarily changing the paths taken historically by the discipline. In the past, chemistry had to contribute to the creation of consumer goods, drugs, and pesticides, while today it must solve the problem of chemical pollution.

This approach has two differences from that proposed by Anastas and Warner (1998). First, it does not focus on the intrinsic risks of chemical production and essentially conceives of pollution as a problem 'external' to the discipline, and somewhat inevitable. The idea of prevention – so prominent in the 1990s sociopolitical context of the United States that 'benign by design' became discussed – was much less present in France during the 2000s, when regulations focused on identifying risks substance by substance, in order to prevent dangerous uses of them. Second, the notion that chemists bear a strong responsibility for risks posed by the use of their products was very diffuse, if not effectively nonexistent. The same is true for the notion of internalizing environmental concerns through training that would better integrate the concepts of toxicity and the life cycle of substances.

3. Green Chemistry and Toxicology, a Relationship Built on Misunderstanding and Force of Habit

From the beginnings of GC in the United States, a special and privileged relationship was envisioned between chemistry and toxicology, especially in its mechanistic aspects. This link was conceptually favored by the central role of toxicology in the regulatory approach of chemical risks, and by the birth of GC in the context of political initiatives for pollution prevention. With help from toxicology, chemists could assess the molecular characteristics that are responsible for the dangerous properties of substances, and thus be able to avoid them in the structures of new molecules. Once the desired function is correlated to a molecular structure, the chemist may modify this structure to limit its potential toxicity or other hazards. To achieve these objectives, several tools are available to chemists, including the analysis of mechanisms of action, structure-activity relationships, avoiding certain functional groups, minimizing bioavailability, or minimizing auxiliary substances.[7]

In the founding work of GC (Anastas & Warner 1998), the pedagogical objective was explicitly defined to the extent that exercises were proposed at the end of the book. To integrate environmental criteria into the research and innovation decisions of chemists, it is important to educate them about toxicology. This had never happened previously, as chemists had little or no training in understanding the biological effects of substances they created, and toxicology classes did not exist in their curricula. The main players in this shift were molecular and synthetic chemists, those with the greatest need to understand the health and environmental impacts of substances in order to conduct their work. In agreement with the general voluntary approach to GC promoted by the book, training in toxicology was considered to be an important contributor to changing chemists' states of mind and hence to promoting the adoption of new research practices.

Despite the apparent simplicity of the proposal, after twenty years of GC, toxicology is barely taught to chemists in American universities,[8] and the situation in France is no different. According to David Constable, director of the American Chemical Society's Green Chemistry Institute, major research universities "are not just blasé about it, they are actually ferociously antagonistic", considering toxicology to be unnecessary in the education of new chemists.

Where is this lack of interest, and even refusal, to learn about chemical impacts coming from? When 'regular' chemists sit down to work at their bench, do they embrace the newly recognized social role stipulated by GC, and the associated moral responsibility? The great upheaval of GC, in its original formulation, concerned the status of the chemist-researcher in the chain between laboratory, industry, consumer, and regulators. Its founders wished for chemists to assume a new power, that of influencing pollution, but do chemists actually do so in their daily work? Simply put, *are chemists living up to the early ethical promise of green chemistry?*

To answer our questions, we conducted a survey of 70 green chemists (34 American and 36 French), from June 2013 to June 2014. Most of our American respondents worked in public academia; two worked in public structures dedicated to GC policies, and one was in a company but had an important background in academia, and one was retired. All but one of our French respondents worked in public academia, and the remaining respondent worked in industry but had diverse experience in public research.

3.1 Do chemists feel responsible for chemical risks?

For the most down-to-earth of our American respondents, adoption of GC goes without much question. Why not, since the borders between what is green and what is not are so blurred? Who can claim that a result declared in accordance with GC is not really so, given the complexity of potential health and environmental impacts and the impossibility of measuring them absolutely?[9]

> So, that's the point when we actually have to say what green chemistry is. I think green chemistry is not a science. I think green chemistry is a philosophy, how you make things. [...] There are no standards [about] what is green. When you came up with something better, it's always green. If you just change again, the water flow in a certain process and you save, let's say 10 000 tons of water, over a year, then you did a nice job.

For others, the new power given to them by GC cannot be applied to all research situations. It concerns only the most applied subjects, and requires that the chemist be in a favorable institutional context:

> If it's fundamental research (...) you can't control. You publish a paper on some aspect on fundamental research, how do you know if somebody is going to take this information and use it to, to design, a commercial product? You have no idea. I mean, it's not like, if you're making an atom bomb, you know exactly how the processes are going to be used. If I'm doing fundamental research on how plastics degrade when they are exposed to sunlight, and somebody comes up with some evil way to use that, I don't know, I don't think that's my fault.

The vast majority of our respondents still believe that risk comes from use (exposure), so as chemists do not control the use, neither can they control the risks:

> I don't think the chemist has that much power. Because, I think first of all, while the chemist is making a decision on the green output of their research [...] it's not necessarily a conscious decision. And secondarily, a lot of times once a product or a process is developed, there will be significant changes in the implementation.

Faced with the question of moral responsibility, the criterion of use prevails over the reference to intrinsic properties, which is specific to early GC:

> Just imagine if you make a molecule. That molecule can be utilized in several ways. If I create something, as dynamite created by Alfred Nobel, his purpose was, I think it was a noble purpose. But, the industry or some people, they used it totally different. I think almost every chemical, if you create in the laboratory, your ambition may be to use for the goodness of the human purpose. But in many cases, that is not the case, maybe 80% of use it's for good ones. But the other 20% may be for something else. Then, who made that de-

> cision? I don't think that it is the responsibility of the creators, because we cannot do that.

Though practically impossible to attain in reality, the principle of limiting danger by working on intrinsic properties suits those chemists who willingly accept it as an ideal and a great educational landmark:

> If you look at what really they're saying is that risk is an equation of exposure times hazard. If you, as a chemist developed something that has zero hazard there will always be zero risk. In that again, there's nothing wrong with these as ideals. They're unachievable. There's nothing wrong with these as drivers.

For several respondents, whether it is GC or other terms, money will always be the main factor to influence chemistry, so responsibility is shared between scientists and research funders.

> And people, if the money wasn't there, they wouldn't be doing it. They do the research and so we have an equivalent amount of funding in green chemistry, everyone who's skeptical now, tomorrow will say I've been doing this all my life, of course this is important'. For another: 'We should do things in a credible and conscientious fashion, instead of following the money, like now.'

Also:

> I hate to say this. There are obviously some people who just believe in the science, but a lot of it ultimately I hate to say, how crass our society is, but mostly […] researchers will follow the money. They wouldn't be, they would be anywhere near as much interest in my opinion, in so called green chemistry, if the research dollars weren't there from the government and the industry.

Finally, another chemist stated that as toxicological tests are very expensive, the companies must be responsible for proving that a new substance meets the regulatory standards.

In contrast with the above views of their colleagues, a minority of chemists, who are in agreement with the initial proposals of GC founders about the role of toxicology, are often close to their direct influence, and work in leading, highly recognized and rather exemplary institutions in the field of GC (*e.g.* Yale University, University of California at Berkeley, Carnegie Mellon University).

Like their American colleagues, few French chemists think they can truly influence the potential impacts of their work on health and the environment. The moral duty is to take an interest in it and to think about it, but it is more a question to be asked, rather than concrete actions that they themselves can take in their research.

> So, I will say that the chemist is not a single person. There are several players in chemistry. So if the chemist […] is a researcher, I do not think he has a responsibility because the researcher's vocation is to create knowledge. Respon-

sibility is that of society, that is to say, either companies that produce and market molecules, or the consumer himself who is going to make an excessive use of these molecules, or the institutions that do not put in place what it takes to monitor the dangers or to recycle, or whatever. So it's a problem that concerns society. The chemistry researcher who creates knowledge cannot be responsible for what is done afterwards with the knowledge he has created. These are the same discoveries that have made it possible to develop the atomic weapon and the MRI for medical imaging, so we cannot incriminate researchers in my opinion for this kind of thing.

Most of our respondents think that they have little control, because their work represents only a small part of the process that will actually be implemented, or of the product that will be marketed. Most of the responsibility for these impacts lies with the employees of the industries who take decisions about production processes:

> I do not think that the chemist, when he makes a plastic material at the beginning, will decree that there will be phthalates inside, which will be then found everywhere. He does not decide this, when he conceives his synthesis on paper. He, will really think about his process of preparing a given molecule. That's for sure. He will think about limiting the impact, especially now. He will try to devise the best possible synthesis process. After that, he will not master any more at all the use of the molecule.

Besides the industry, the user is also viewed as being responsible:

> […] stories like Bisphenol A, I mean, it's not a problem of chemists, it is the problem of the use of chemistry by the public. When you see the farmers, the way they handle pesticides […] the training is not there, it's clear.

The path between the laboratory and the market is very long:

> If you look at the liquid crystals of De Gennes, he did not know that it would be one day used, when he invented them. We had to wait, I do not know how much, fifteen, twenty years[…].

In addition, knowledge about health risks is also changing, therefore impacts that could not be guessed are discovered long after a substance has been discovered or placed on the market. According to this view, the acquisition of knowledge in these areas cannot be foreseen.

Not only are they not masters over the final risk of their work, but they are also reluctant to embrace the need to minimize the possible impacts. A good idea that solves a problem can first be built from building blocks that in themselves have a significant impact on health or the environment, but that might then be improved by other colleagues in the future, so that the impact might be ultimately limited:

> And then, it's true that on the bench, if at some point something works, and then you have to put a solvent that is not terrible, but with that it will go fast-

> er, we are still at the level of the bench. And so, if we can accelerate something, a process, if we can make an even more exotic material, if we think that the applications will be good, we will not deprive ourselves either. Finally I mean, we are not Stakhanovists of the green anyway. We will try to remain realistic. That does not prevent from improving later and start over.

> When one is going to do fundamental research, one should not refrain from using certain synthetic paths that are not clean. Sometimes, for understanding, one is obliged to go through steps that are not green and therefore we should not say that, because we want to have a green chemistry label at all costs, we will refrain from having access to things that may be less clean. But it's going to be punctual, we know it very well and in this case we take the protections that are necessary to avoid having any concern, but I think we shouldn't start by saying that on paper it's not good, so we stop everything […] But if it's for the fundamental aspect, where we know that it will not go out of the lab because it is only to understand a mechanism, to understand an interaction or things like that, we should not start by saying, there is something, it is dangerous, there will be waste […] Yes it is dangerous, yes there will be waste, but well we know how to manage it.

Whereas work with toxicology has to be interdisciplinary, the great majority of respondents think it is beyond their competence to be concerned with toxicity issues, so their viewpoint is focused narrowly on the distinction among disciplines: "There are people who are specialized in this, who are going to look at this kind of thing." Finally, toxicity is studied once the substance or process has been developed, by toxicologists and often in a regulatory context, which according to our respondents is rigorous enough to ensure public protection. Therefore, the responsibility for the treatment of toxicity lies, in addition to industry and consumers, with toxicologists and regulatory authorities. Chemists do not really have a say or influence in this matter.

3.2 The fragile place of toxicology in green chemistry

Feedback from our respondents showed that the role of toxicity in defining the 'green' character of a substance or process is vague and marked by contradiction. For example, whereas catalysis is considered to be "the foundational pillar of green chemistry" (Anastas *et al*. 2001), some catalysts are also toxic. Should all the work on catalysis therefore be labeled 'green chemistry'? Referring to a bio-based polymer such as polylactic acid (PLA) an American respondent argues:

> when you look at the synthesis and the synthesis that is published uses organotin, that's a toxic catalyst. There are steps that use heptane, it's a sort of solvent that you don't really want to use. So there are non-green things that are used along the way to come up with the green products.

Ionic liquids make another good illustration. They allow the replacement of organic solvents whose toxicity is recognized, but some are also toxic. In this situation, some of our respondents return to the classic pattern of thinking about risks by focusing on exposure control. If the conditions for use of ionic liquids are under control, their toxicity is also under control.

A third example is nanoparticles, which some chemists are willing to integrate into the field of GC (*e.g.*, they serve as catalysts for the production of biofuels or as support for biocidal treatments in forests), but without referring to their potential (eco-)toxicity. For a French respondent:

> Well, I mean us, we also work on nanocatalysts, nanoparticles and so on, and I have to confess that we haven't thought about their toxicity yet.

While it played a leading role at the beginning of GC's promotion by Anastas and Warner, accounting for the toxicological properties of new substances at the design phase is currently often ignored. Chemists consider that the sciences dealing with the impacts of chemistry on the environment and health are scientific disciplines of their own. Chemists can teach toxicologists, pharmacists, biochemists, or doctors, but toxicity would not be part of their own work:

> Pharmacy is nevertheless a science that is very much linked to the activity of molecules. So these people actually know the activity, and therefore the toxicity. And so, they can certainly afford to have this reflection and anticipation. But us, we are really focused on properties, I will say especially on materials, or on reactivity with other functions. So we know that if we put a group here or there or not, the reactivity will evolve, but we will have the reactivity with other molecules in fact. For an organic chemist, I would say, who is basically a polymerist, this is what interests him most. So that's why it's still not obvious, unless to search for information, but one will not have a predictive vision as extensive as a pharmacist or a toxicologist.

For another one:

> I typically do not have these, I do not have those skills in tox and ecotox typically, it's something I'm aware of, I'm aware that when I develop a molecule it's going to be one of the criteria that I'm going to have to study, but it's something that I subcontract very willingly. […] At the same time, we cannot do everything, we cannot be a specialist everywhere.

3.3 Are chemists working with toxicologists?

Among the chemists interviewed, few work with toxicologists. All those with such collaborations, who were a minority, belong mainly to teams recognized in the United States for their work in GC, including the Berkeley Green Chemistry Center, the University of Oregon, or teams working with people such as Paul Anastas, John Warner, and Terry Collins, who have always supported the idea of bringing chemistry and toxicology closer together. At the level of the other 'basic' green chemists, this connection has yet to be made, for if it is generally considered appropriate and necessary, in practice it does not take shape.

For one American chemist who failed at trying to work with a toxicologist, the cause was essentially the difference in approach and valorization of the research of each partner. According to him, while chemists believe that they need someone to evaluate the toxicity of the substances they use, as a consulting firm would do, toxicologists consider this work to be too applied and are interested in much more fundamental, theoretical developments in their discipline. In addition, large research funding agencies are targeting much more innovative scientific developments, while simple, routine toxicological tests are difficult to fund. When approaching the toxicologists, our chemist respondent envisaged an intervention of this discipline downstream of his own work. Whereas to the founders of GC, toxicology is integral to GC and must contribute to it throughout any reflection about new syntheses, for this respondent the approach is much more conventional. First, the chemist does the work. Then, the toxicologist assesses whether this work has environmental and health impacts. It is not viewed as a partnership.

Third, it would also appear that different publication practices govern the two communities, with a high degree of publication bias. In any case, that chemist thinks that toxicologists are more likely to see their work published if the substances they assess are toxic, whereas a chemist's objective is precisely to use or develop substances with reduced toxicity. For this reason, toxicologists' interest in working with green chemists would be reduced.

But one of the most important problems would be the difficulty of obtaining new substances that present less toxicity:

> I mean, most, certainly, most people who design new chemicals are organic chemists and most of them know what make its toxic. Ok, because they know what makes it reactive, so that's the thing. And that's even part of the problem with chemistry, is that, in order to make it reactive, that's what makes it toxic in most cases.

Another American respondent talked about cultural differences between the two communities:

> I mean it's very common to say 'Oh, I'm a chemist, I'm not a toxicologist' and 'I'm a toxicologist, I'm not a chemist'. So overcoming that cultural barrier and saying 'Well, ok maybe, I'm not a toxicologist, but I should know something about toxicology'. That step is not really here.

These gaps seem all the more difficult to overcome as the current organization of the academic system does not favor rapid change or interdisciplinary collaboration:

> you know change in university is very slow, so it's hard to, you know, connect the chemistry department to, like the public health department or something.

Partnership between chemists and toxicologists or ecotoxicologists is also rare among French chemists. Only 7 out of 36 of our French interlocutors have already worked with these disciplines, *i.e.* with ecotoxicologists to estimate the dangers of nanoparticles or the ecological restoration capacities, to develop biomarkers, to assess the impact of certain remediation solutions on water quality, or to assess in vitro toxicity.

Such collaborations are rare for many reasons. First, our respondents do not see relations with toxicology as part of their own work, but rather consider that these are two different disciplines, with distinct vocabularies. Moreover, the two communities are not used to working together historically, which leads to an absence of common networks, a lack of opportunities for joint publication or funding, and different methods for evaluating the researchers' careers. Lastly, there would be a deeper incompatibility with toxicologists, in terms of research objectives, because they focus on identifying a no-effect dose. Nevertheless, what interests the chemist is the molecular mechanism of toxicity. Essentially an applied discipline that intervenes at the end of a research chain once the molecule is synthesized, toxicology would thus have no other interest for the synthesis chemist beyond providing a service. Its role would be to verify whether the properties of a newly synthesized molecule that could be marketed correspond to health and environmental regulatory standards. This shows that the two disciplines do not know each other, and that chemists easily confound academic and regulatory toxicology.

Because toxicology is considered as the end of chemistry's research chain, and as a service intended to assess whether the work respects regulatory norms, many of our respondents consider it to be an additional constraint that is often expensive and uninteresting for toxicologists themselves, and not as an opportunity to develop new ideas in their own field of research.

4. Discussion and Conclusions

Since its very beginning, GC was formulated as a question of chemists' ethical responsibility towards humanity. One of the first to have used the term, even before the field's founders, was Kenneth Hancock, former director of the Chemistry Division of the U.S. National Science Foundation (NSF). After stating "Whether you are talking about oil spills, or landfills, or ozone holes [...] or any [human-made] environmental problem that has ever occurred, it comes from chemistry" (Amato 1993, pp. 1538), he framed those problems as opportunities for chemists: "Any solution that you will devise will come from chemistry". The early ethical formulations of green chemistry presented chemists' moral duty towards the health of their citizen fellows – which is often a constraint – in a positive and attractive manner. Avoiding sanctimonius positions that would likely raise resistance among conservative chemists, GC essentially took the form of a scientific challenge, while its fundamentals were clearly ethical: whatever the interest for the research, above all, do not harm humans and other life on the planet.

After historical misuses, other disciplines have taken similar action to set clear limitations about what is morally acceptable in the realm of scientific work. After the Nuremberg trials, the World Medical Association adopted and regularly renewed the Declaration of Helsinki, which established ethical principles for the conduct of medical research on human subjects. Other professional and academic associations (*e.g.*, in sociology, psychology, and educational sciences) adopted similar codes of ethical conduct. In all disciplines, ethical research has become a priority for funding research at the European Commission.[10]

Since the 1990s, while chemists have seized the opportunity of GC for renewing their research and conceiving it in new terms (bio-based chemistry, catalysis, new solvents, *etc.*) according to some of the twelve principles, thereby successfully using interdisciplinary collaborations (Rico-Lattes & Maxim 2014), the use of toxicology for reducing the toxicity of molecules and processes remains very weak.

Indeed, as Anastas and Zimmerman (2016b) recently stated, designing safer chemicals "is no small feat", toxicity endpoints are numerous and heterogeneous, ranging from carcinogenicity to reproductive toxicity and endocrine disruption. Enthusiastically, these authors concluded: "Good thing that chemists didn't go into this field because it was easy." Driven by the hope that repetition will end by producing a change in their colleagues' mindsets, such optimistic pushes have characterized GC's leaders and some of their followers since its very beginning. Despite these repeated calls for change, some other chemists still remain tied by the forces of habit and skepticism, whereas many others feel trapped in institutional settings. In this light, the results from the interviews are not so astonishing. While not trained in toxicology, and being stuck in an academic system that in practice strongly discourages interdisciplinary research (despite institutional discourses stating the contrary), few chemists, be they green or not, are able (or willing) to individually transcend their own education and embrace toxicology along with their moral responsibility for chemical risks. Complementing the other GC paper in this issue (Iles *et al*. 2017), we could call this an 'academic lock-in' for which the locks are peoples' minds, those people who assess colleagues' work regarding their employment, funding their research, accepting their communications in conferences, and/or publishing their research. Such people who advise funders on the directions for research priorities, figure in the hierarchies of universities and research centers, who give and receive medals and prizes for research, also hold the power to promote a message to the global chemistry community. The conceptual and technical opportunities clearly exist for using toxicology in chemistry, as some research teams have demonstrated through their projects and publications (*e.g.*, Beach *et al*. 2013, Corrales *et al*. 2016, Shen *et al*. 2016, Faulkner *et al*. 2017).

Green chemists and toxicologists do not know each others' work, though solutions for overcoming this situation are known. Examples include joint workshops and conferences, funding for joint calls for projects and research proposals, and building procedures for sharing data between the two disciplines, removing terminology barriers, and creating joint journals (Zimmermann *et al*. 2014). Provided that chemists overcome skepticism and approach their science with enthusiasm, GC provides an extraordinary opportunity to leave behind the negative image of their science that formed in the public over history (Schummer *et al*. 2007). The biggest danger for chemistry's social status is the opportunistic use of 'green' by some chemists that ends up destroying the potential for real work with toxicology, and downplaying the fragile emergence of a renewed science, turned towards society (understood in a larger meaning than a sum of consumers).

The ethical case of chemistry is more difficult to address directly, compared to the case of medical sciences, as chemists do not consciously 'experiment' with the effects of chemicals on humans (whilst in reality, they nevertheless do!). Furthermore, these effects are insidious, multiple, sometimes appearing long after exposure, and entrenched in multiple exposures – factors that facilitate the task of doubt promoters. However, working on a code of research ethics might enable the chemists' community to enrich the pragmatic significance of the twelve GC principles for bench work, and explicitly put on the table the importance of working with toxicology.

Woodhouse (2005) compared chemistry with a form of legislation that influences the daily life of billions of persons, which would call for a level of accountability equivalent to that of any other decision-maker in democracies. While the situation seems hard to change, in the minds of 'mature' chemists, younger generations represent hope for a less polluted world in which chemists do their best to preserve the health and lives of fellow citizens, instead of saying that someone else – toxicologists, industry, regulators, consumers, *etc*. – should deal with it. The majority of our respondents told us that their students in chemistry are strongly motivated by GC, and some respondents even learned about GC from a student, while others started to address GC in response to student demand. GC might have finally reached a point where it can do better than recycling older research on bio-based chemicals, nanotechnology, or catalysis, and try something newer, and more challenging, meaningful, and certainly more difficult, like developing benign-by-design molecules and less toxic processes.

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Notes

1 These authors defined GC as "the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture and application of chemical products" (Anastas & Warner 1998, p. 11).

2 Green chemists are divided on whether regulation should be used, as shown for example by the debate published in *Environmental Health Perspectives* (2009) between Wilson & Schwartzman and O'Brien, Meyers & Warner.

3 While documented for the chemical industry, we will not discuss here the accuracy and relevance of this formula for academic chemists, which has been done elsewhere (Bensaude-Vincent 2005, Schummer *et al*. 2007, Maxim 2011).

4 He later became President of the biggest research center in France, the National Center for Scientific Research (from 2010 to present, *i.e*., May 2017).

5 Similarly, the events organized in 2011, which were labeled the 'Year of Chemistry' by UNESCO, aimed at "celebrating the contributions of chemistry to the welfare of mankind" (UNESCO 2011, p. 2).

6 Quoted from the CNRS website, Description of the research program 'Chimie pour le développement durable' [available online at: http://www.cnrs.fr/prg/PIR/programmes/IngECOTech/cpdd/chimiedevptdur.htm, accessed 23 August 2017].

7 DeVito and Garrett (1996) proposed to go even farther, towards a chemistry that synthesizes substances adapted to the functioning of living beings. These substances would be easily metabolized and excreted, or would not be bioavailable. This proposal was inspired by the pharmaceutical chemistry that builds its molecules based on sound knowledge of how they behave in the human body. Even if the pharmaceutical branch of chemistry already practiced this principle, the change it proposed was radical for industrial chemists.

[8] https://www.chemistryworld.com/news/green-chemistry-hindered-by-lack-of-toxicology-training/9358.article.

[9] All unreferenced quotations below are from interviewees.

[10] See for example European Commission 2013.

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