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Genomic Misconception: a fresh look at the biosafety of transgenic and conventional crops. A plea for a process agnostic regulation

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The regulation of genetically engineered crops, in Europe and within the legislation of the Cartagena biosafety protocol is built on false premises: The claim was (and unfortunately still is) that there is a basic difference between conventional and transgenic crops, this despite the fact that this has been rejected on scientifically solid grounds since many years. This contribution collects some major arguments for a fresh look at regulation of transgenic crops, they are in their molecular processes of creation not basically different from conventional crops, which are based in their breeding methods on natural, sometimes enhanced mutation. But the fascination and euphoria of the discoveries in molecular biology and the new perspectives in plant breeding in the sixties and seventies led to the wrong focus on transgenic plants alone. In a collective framing process the initial biosafety debates focused on the novelty of the process of transgenesis. When early debates on the risk assessment merged into legislative decisions, this wrong focus on transgenesis alone seemed uncontested. The process-focused view was also fostered by a conglomerate of concerned scientists and biotechnology companies, both with a vested interest to at least tolerate the rise of the safety threshold to secure research money and to discourage competitors of all kinds. Policy minded people and opponent activists without deeper insight in the molecular science agreed to those efforts without much resistance. It is interesting to realize, that the focus on processes was uncontested by a majority of regulators, this despite of serious early warnings from important authorities in science, mainly of US origin. It is time to change the regulation of genetically modified (GM) crops toward a more science based process — agnostic legislation. Although this article concentrates on the critique of the process-oriented regulation, including some details about the history behind, there should be no misunderstanding that there are other important factors responsible for the failure of this kind of process-oriented regulation, most importantly: the predominance of politics in the decision making processes combined with the lack of serious scientific debates on regulatory matters within the European Union and also in the Cartagena system, the obscure and much too complex decision making structures within the EU, and the active, professional, negative and intimidating role of fundamental opposition against GM crops on all levels dealing with flawed science, often declared as better parallel science published by 'independent' scientists.

The scientific basis of the process agnostic regulation

Genetic engineering has been brought into evolutionary perspective of natural mutation by authorities such as Werner Arber: his view, already published in 1990 and downloadble from SCOPE [1] remains scientifically uncontested that molecular processes in transgenesis and natural mutation are basically similar [2]. In two recent papers, Arber [3,4] re-emphasized those similarities on a broader organismal and evolutionary basis.

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Arber notes [5]:

"Interestingly, naturally occurring molecular evolution, i.e. the spontaneous generation of genetic variants has been seen to follow exactly the same three strategies as those used in genetic engineering. These three strategies are:

(a) small local changes in the nucleotide sequences,
(b) internal reshuffling of genomic DNA segments, and
(c) acquisition of usually rather small segments of DNA from another type of organism by horizontal gene transfer."

Fifteen years of intensive biosafety research have diminished those concerns considerably as mentioned by many specialists, including the Public Research and Regulation Initiative (PRRI) in several letters to the European and International regulatory agencies, as an example a letter from September 14, 2009 [6], which also insists on a process agnostic regulation of genetically modified (GM) crops. Until now the reaction of the authorities on the European and international level was and is clearly insufficient.

There are proofs of political pressure from green activists and parties [7] for this process based regulation, astonishingly enough excluding also forced mutagenesis for example. Since the first establishment of the process focus in GM crop regulation in the early 2000s, a very strong lobby with important influence on the European and the UN level fights for even tighter regulation related to the marketing of 'genetically modified' (GM) crops. The regulatory rules have been strengthened continuously due to political pressure, not just in the EU but also in other countries such as India, for example [8,9]. The 'precautionary principle' has acquired the status of a doctrine in EU regulation, but actually should be renamed to its legal term 'precautionary approach' with its clearly different and more open minded meaning [10–12]. According to Durham *et al.* process agnostic regulation needs to be considered seriously in the future [13], it should furthermore also include a de minimus approach, the authors call for more balance in regulation: Whereas only a minimal number of GM crops got approval in the US going through excessive regulation, thousands of non-GM crops have been cleared with little, if any regulatory scrutiny, clearly a situation not in balance with actual experience in a risk comparison between transgenic and conventional crops.

Understanding the molecular basis of the process-agnostic regulation makes it also easy to accept the fact that transcriptomic disturbance in transgenic crops is less important than in conventional crops, numerous papers gave proof [14–19], and more: natural variation of conventional crops is often more important than genomic variation of transgenic crops [20,21]. However, precise transcriptomic analysis has also revealed that non-uniform distribution pattern for differentially expressed genes of transgenic rice Huahui 1 at different developmental stages and environments: Liu *et al.* [22] — this clearly demonstrates, that the learning process in molecular genomics will go on — and will give prove that regulation of GM crops needs more science based flexibility — it should however be clear that the new results of Liu *et al.* have no direct relation to biosafety issues. Because of the persistence of the Genomic Misconception myths are also growing that GE crops have more unintended effects than conventional crops, this has been falsified properly by important publications and reports such as the book coming from the National Academy of Sciences [23], clearly stating:

"In contrast to adverse health effects that have been associated with some traditional food production methods, similar serious health effects have not been identified as a result of genetic engineering techniques used in food production. This may be because developers of bioengineered organisms perform extensive compositional analyses to determine that each phenotype is desirable and to ensure that unintended changes have not occurred in key components of food."

However, in exceptional cases like the one on GE peas from Australia which showed altered structure and immunogenicity, so that the research team concluded not to pursue the case anymore for food applications, although it was revealed later that the new structures were non-allergenic [24,25].

It should also be made clear, that food as a result from GE or conventional crop breeding show the same metabolic complexity, so that reductionist conclusions will always fail [26].

How the Genomic Misconception was evolving

In the wake of molecular genetics Avery *et al.* [27] wrote about their historic discovery of DNA as the molecule uniquely associated with the storage and transfer of genetic information between different strains of bacteria (see the comments of Lederberg about the importance of this discovery by Lederberg [28]).

The biosafety debates started soon after the discovery of the DNA double helix structure by Watson and Crick [29–31], and Wilkins *et al.* [32], the history of the groundbreaking discovery is treated in Glickstein, Olby and Vasil [33–35] and the major account in Watson and Tooze [36]. The justified euphoria also led to impressive perspectives about the new possibilities to manipulate living organisms. Later, Cohen *et al.* [37,38] discovered successful ways of 'gene splicing' by the construction of new biologically functional plasmids in vitro through joining cohesive-ended plasmid DNA molecules of entirely different origin. The same authors also predicted that these general procedures could be used for the insertion of specific DNA sequences from prokaryotic or eukaryotic chromosomes or extra-chromosomal DNA into independently replicating bacterial plasmids. These transfer methods have been constantly refined and made more efficient and safer [39–41]. Another breakthrough was initiated by more and more efficient DNA sequencing methods, starting with Sanger *et al.* [42] and continued by Maxam and Gilbert, and Smith and Birnstiel [43,44].

In a first debate phase, biosafety concerns were predominant among a majority of leading scientists. Under the impression of the many unknowns in the pioneer phase, concerned scientists called for an international conference on biosafety related to recombinant DNA [45], which was then organized by an international committee: The well attended conference took place in Asilomar, California with the task to discuss potential risks of the new technology [46–50]. According to Zinder [51] the US debate was divisable in Asilomar (1974–76), the 'recombinant DNA wars' (1976–78), summarized in Zilinskas and Zimmerman [52] and the subsequent détente period.

The times of the '*recombinant DNA wars*' were accurately reflected by the first very strict guidelines issued by the National Institute of Health, but they did not mark the end of the discussions [53]. The crucial first phase is also well mirrored by a letter of EMBO to the National Institute of Health [54], concerns were numerous but the letter also warns against tightening further the safety rules, in particular the rules on containments for diverse experiment risk levels.

According to Cantley [55] the US debate, starting with full speed in 1976, made step by step good progress, and entered after the hefty debates from 1976 to 1978 into a period making use of a rapidly growing molecular insight, and consequently replacing unfounded concerns with confirmed and precise science, thus easing down the conflicts in a period of détente.

"A major feature of the debates in the US was the progressive development of a well-organized, articulate and balanced response by the scientific community. The leading role was played by the American Society of Microbiology (ASM), but many other professional associations of biological and medical sciences joined with ASM in a broad alliance, through semiformal linkages via their executive officers, and widespread networks capable of providing rapid responses." ***[55].***

But it should also be made clear that the US debate suffered from many problems: As the ASM (American Society of Microbiology) expressed strong criticism on the debate at hearings in November 1977, *Source*: Halvorson [56,57]

"The apparent intemperate rush to establish legislation to regulate recombinant research without first consulting with the appropriately qualified scientific and medical experts, the need to understand that early allegations concerning recombinant DNA research were characterized by uncontrolled imagination and excessive claims by individuals who lacked knowledge of infectious disease, and the need for minimal interim legislation to extend appropriate guidelines to all recombinant DNA activities regardless of funding source." ***[56,57]***

Solutions were achieved thanks to an open and earlier debate, also due to the fact that authorities and congress in the US demonstrated a remarkable ability to learn in the same pace as scientific knowledge was growing. Deepening molecular insight enabled a better understanding of transgenesis. This was more dynamic in the US, and earlier than in Europe, not due to better science, but because of the more adequate discursive structures. Another important difference in this opening transatlantic divide is hidden in the differences of major political structures, that is, between a United States of America against a much less centralized European Union with clearly hampered decision making processes and debate structures as clearly diagnosed as obscure, too complex and deeply dysfunctional by a new study done by independent experts for DG Sanco [58], the result of major delays, in some cases for years, in the approval of GM crops are obvious [59].

Finally, the US came to a solution in regulation of GM crops which holds up in the main lines until now, this is due to the efforts in the regulatory system, as summarized by Tooze, Harmonizing Guidelines [60].

How the 'Genomic Misconception' was erroneously maintained in the European regulation and the Cartagena Protocol on Biosafety

Europe, the development of the transatlantic divide

Support of a process-agnostic view (today followed by only a few states like the United States and Canada) has been published in official letters of European Scientists, including 16 Nobel Prize Laureates, they warned against a legislation targeting the process (transgenesis) alone and not the product itself (its traits), a regulatory erroneous principle which can be called '*Genomic Misconception*'. The scientists unanimously stated (full text from Cantley [55]), bold from the author:

"Dear Mr. President,
In the fourth week of May the European Parliament will debate in Plenary Session a subject which ***is*** *of vital importance for the future development* ***of*** *science in Europe, namely the three Commission proposals for Council Directives on biotechnology. The Council will decide on this matter at the beginning of June.*
Recombinant DNA is a method in biology, without which modern research in this field is not possible. It allows small and well defined changes to be introduced into the genomic set-up of an organism. More than 90% of research and production use non-pathogenic and safe organisms. There are well established and internationally accepted safety standards which have been followed by a community of about one hundred thousand researchers in the past 15 years. The EC Commission has proposed three Council Directives, based on this experience. ***In principle there is no scientific justification to single out a technique for regulation instead of basing it on the properties of the generated organisms****. Consequently, the proposal on 'Worker Protection' relates to '. . .Exposure to Biological Agents' irrespective of the method by which these agents may have obtained their characteristics. The proposals on 'Contained Use' and 'Deliberate Release' of genetically modified organisms are in line with already existing OECD recommendations and the guidelines o f a number of major countries, such as the USA and Japan.* ***Amendments have been proposed which are based on unfounded fears rather than on scientific risk assessment. They are both impractical and widely inhibitory to the progress of knowledge and its responsible beneficial applications.*** *We refer in particular to those tabled by the rapporteurs for the Environment, Public Health, and Consumer Protection Committee. as well as those accepted additionally in the same committee.*
We would therefore appeal for your support for the Commission's proposals, un-amended in this important debate."

From ***[55].***

Unfortunately, European authorities did not consider the timely recommendations of the Nobel laureates, and they also ignored advise by the US National Academy of Sciences as early as 1987 [61] with a clear message in favor of a process agnostic view in regulation, strictly based on the general insights in molecular processes:

"There is no evidence that unique hazards exist either in the use of R-DNA techniques or in the transfer of genes between unrelated organisms", ***and:***
"The risks associated with R-DNA engineered organisms are the same in kind as those associated with the introduction into the environment of unmodified organisms and organisms modified by other genetic techniques."
And:
"Assessment of the risks of introducing R-DNA-engineered organisms into the environment should be based on the nature of the organism and the environment into which it will be introduced, not on the method by which it was modified."

The subsequent consolidated report of the US Academy of Sciences from 2000 [62] explicitly maintains this process agnostic view, widening the perspective to health and environmental risks involved and admitting that research lacunes should be covered in the future:

"Although the same scientific arguments can be made for the risks posed by conventional pest-protected plants, which are not subject to regulation under the coordinated framework, lack of experience with transgenic pest-protected products and public concern with these products constitute practical reasons for not granting a categorical exemption to transgenic pest-protectants derived from sexually compatible species."

It did not have any impact on European regulation, despite numerous publications in the US: according to Cantley [55] these developments were watched with growing alarm by scientific and industrial circles, in Europe and elsewhere in the world. In several publications in important science journals (indeed hard to oversee...) the Commissioner of the US Food and Drug Association (Young) and his special assistant (Miller) had explicitly criticized the Commission's proposed Directive on field release. On three grounds [63–65] and cited below [7]

- *''the underlying premises on which it was based;*
- *the risk of a regulatory approach that would hinder research and development;*
- *the possible use of its provisions to erect non-tariff trade barriers to foreign products.''*

Developing the first point, they noted that:

"The directive is focused on the regulation of 'genetically modified organisms (CMOS)', which are defined as those manipulated with only certain recently developed techniques, including recombinant DNA. Thus the directive preferentially singles out for stringent regulation the newest techniques of genetic manipulation that enable the most precise and predictable genetic changes. This is at odds with the broad consensus that these newest techniques represent a clear refinement, an improvement on conventional techniques of genetic manipulation that enhances the precision and predictability of the effects of intervention.
Such GMOs are clearly not a functional category. and most certainly not one correlated to risk." ***[7]***

The first scientist organizing GM crop regulation in the US Henry I. Miller criticized strongly over many years and with dozens of publications in science journals the focus on transgenesis in regulatory procedures, a selection [66–72], all ignored by the European authorities. There would be much more early voices stating the same like Halvorson [56,57].

Regulatory authorities in Europe and the United Nations (conceiving the Cartagena Protocol on Biosafety) obviously decided right from the beginning to ignore scientific information supporting the process *agnostic* regulatory approach. They go instead for a strong focus on the process of transgenesis, thus following the British approach from 1978. They followed earlier advice from EMBO, the European Molecular Biology Organization which followed a cautious strategy, not mentioning the genomic misconception problems [54].

Also a second letter of Nobel Prize Laureates pleading against the focus on the process of transgenenesis was again blatantly ignored by the European authorities, much more details can be seen in Cantley [55] and in the Czech White Book [73]. From the same White Book source: No wonder, that a clear statement against process-oriented regulation by a major research association EMBO has been systematically ignored as well: The 40th meeting of the Council of EMBO on the 1st October 1988 discussed the flawed drafts of European regulation and came unanimously to the opinion:

"...that any legislation should focus not on the technique but on the safety or otherwise of the products generated with it. ...Over the last 15 years, experience has shown that recombinant DNA methods, far from being inherently dangerous, are an important tool both for understanding properties of life and for developing applications valuable to humankind and the environment. EMBO strongly believes that there is no scientific justification for additional specific legislation regulating recombinant research per se. Any rules or legislation should only apply to the safety of products according to their properties, rather than according to the methods used to generate them."

This statement was presented to the European Parliament on 16 May 1989 by Max Birnstiel, then the head of EMBO Council, and by Lennart Philipson, the Director General. However, science lost the battle with the European regulators and the 'method is risky and transgenesis is the only one of this sort' was accepted, cementing the Genomic Misconception source: Czech White Book [73].

It is likewise inexcusable, that joint statements of scientific authorities such as the one published in [74] under the lead of Werner Arber were completely ignored [75]

"In view of the great potential of new technologies for addressing environmental and other problems, and because most introductions of modified organisms are likely to represent low or negligible ecological risk, generic arguments against the use of new genetic methodologies must be rejected. Indeed, the spectrum of available tools represents an evolving and expanding continuum, which includes conventional methods, rDNA techniques, and others. While much attention has been focused on the methods used to modify organisms, it is the products of

these technologies and the uses to which they will be put that should be the objects of attention, rather than the particular techniques employed to achieve those ends." **[75]**

The list of co-authors in this declaration is impressive: Arber, W.B.G., Brom, S., Campbell, A., Caplan, A., Cherif-Zahar, B., Christiansen, F.B., Crawley, M.J., Davila, G., Drake, J.A., Dwyer, D.F., Faust, R.M., Fenner, F., Flores, M., Goursot, R., Jayaraman, K., Kingsbury, D.T., Levin, D.T., Martinez, E., Melis, R., Mooney, H.A., Palacios, R., Pinero, D., Rayko, E., Romero, E., Skalka, A.M., Timmis, K.N., and Van Montagu, M. — all the more it is baffling to see this important statement completely ignored in the Cartagena negotiations — one can only wonder over the reasons — the most plausible combination of reasons is the lack of scientific expertise and the influence of green political activists.

About the transatlantic divide there are general descriptions about the dispute published, two examples may suffice:

Legislative history of the Cartagena Protocol and its Genomic Misinterpretation of transgenesis

The author communicated with many of the first hour participants in the negotiations of the Cartagena Protocol on Biosafety [76]. The most notable details come from Prof. Alexander Golikov, member of the Russian Academy of Sciences and executive secretary of the Black See Biotechnology Association (BSBA), see his active website http://www.bsbanet.org/.

During the first session of the biosafety working group creating the Cartagena Protocol on Biosafety (22–26 June 1996 in Aarhus, DK), Prof. Alexander Golikov was the rapporteur of the inaugural expert group (*Biosafety Working Group — BSWG-6*). Golikov explicitly warned the working group (oral communication) not to follow the strict process-oriented regulation of GMOs, which was clearly ignored — and also not mentioned in the summary comments looking back to the decision making process [77]:

"It is possible only to guess the reasons why the negotiations failed in 1999, but succeeded one year later. A group of countries, the so-called 'Miami Group', consisting of Argentina, Australia, Canada, Chile, the US and Uruguay, blocked the finalization of the negotiations in 1999. At the WTO meeting in Seattle at the end of 1999, Canada and the US tried to further a decision on the creation of a working group on biotechnology. This attempt, which was regarded by a number of other countries as an attempt to 'kill' the suspended negotiation on the Biosafety Protocol, failed because of resistance from EU countries. Over 1999, growing skepticism towards products derived from gene technology and biotechnology had also been seen in countries such as Australia, Canada and the US." **[77]**

Nevertheless, the conflicts were substantiated in a detailed way by [78], where trade political reasons are enumerated — without mentioning the genomic misconception — throughout the text is was taken for granted by the authors, that the focus of the biosafety protocol concentrates on LMOs (Living Modified Organisms, thus excluding all products 'Thereof').

"Throughout the negotiations, the Miami Group opposed provisions that would allow governments to subject commodities to advanced informed agreement procedures or documentation requirements (both of which are discussed more fully below) as these obligations would require segregation of LMOs from traditional agriculture products." **[78].**

About the negotiations, Hagen and Weiner published some details:

"The BSWG (Biosafety Working Group) met a total of six times, beginning in July 1996, and concluded its work in February 1999 at its sixth meeting (BSWG-6). Over one hundred governments, including the United States, participated in the negotiation of the Draft Protocol. In accordance with Decision IV/3 of the COP, the BSWG completed a controversial draft text (the Draft Protocol) in Cartagena and referred it to an extraordinary meeting of the COP (Ex-COP) for possible adoption. The Ex-COP opened February 22, 1999 in Cartagena, Colombia. However, disagreements concerning central features of the Draft Protocol, particularly concerning its scope and impact upon trade in GMOs, proved insurmountable. Unable to arrive at a text acceptable to all 134 CBD Parties in attendance, the COP decided to suspend the extraordinary meeting and reconvene no later than COP-5, scheduled to occur in May 2000." **[78].**

The 'Genomic Misconception' was as an important issue discussed in transatlantic debates *long before* the Cartagena Protocol negotiations started, and it was clearly one of the major transatlantic disputes, as [79] document with the dispute on European biosafety research activities: Crawley decries '*arm chair assessment which formerly passed for ecological analysis*' by non-ecologist '*pundits*' who believed that '*a small transgenic change to genotype would have no impact on phenotype*'. However, the arm-chair assessors and pundits are, in this case, an impressive lot, and they include the U.S. National Academy of Sciences [80], the British House of Lords Select Committee on Science and Technology as well as several other international panels and professional groups. The broad scientific consensus was clear and compelling: '*no conceptual distinction exists between genetic modification of plants and microorganisms by classical methods or by molecular methods that modify DNA and transfer genes*,' is compelling. This broadly accepted opinion was based on the ability to extrapolate from general scientific principles (especially those derived from the knowledge of the biological world and from the understanding of evolutionary biology). These concepts served to remind everybody that they were derived from scientific experiments build upon one another and that real progress is not achieved with trivial confirmations. Lets hear what a leading ecologist had to say in these early debates on regulation of GM crops:

Crawley for instance agreed with this opinion above, citing among others the statement of the Ecological Society of America [81]:

"Genetically engineered organisms should be evaluated and regulated according to their biological properties (phenotypes), rather than according to the genetic techniques used to produce them."

And some paragraphs later Tiedje states:

"Transgenic organisms can be designed to minimize the chance of environmental perturbations. The choice of the trait and parent organism used, the form of the genetic alteration, and the control of its expression all affect the likelihood that the genetically engineered organism will have undesirable effects. In addition, the conditions of the organism's introduction can be planned to minimize potential problems. Thus, we believe that with careful design of transgenic organisms and proper planning and regulatory oversight of environmental releases, the introduction of many transgenic organisms can be carried out with minimal ecological risk." **[81]**

But this should according to the authors Tiedje *et al.* not be understood as a call for complete deregulation, as they also emphasize:

"Although we support the timely development of environmentally sound products through the use of advanced biotechnology, we believe that these developments should occur within the context of a scientifically based regulatory policy that encourages innovation without compromising sound environmental management." **[81]**

In his own words, Crawley published in the SCOPE/COGEN volume [82]:

"There seems to be a view that the ecology of genetically engineered organisms is somehow different — more inscrutable perhaps, but certainly more dangerous — and that the intentional release of genetically engineered organisms poses more of a threat to the balance of nature than other kinds of organisms bred by man. This view is mistaken. While there are risks associated with the introduction of any novel organisms into a habitat, the ecology of genetically engineered organisms is exactly the same as the ecology of any other living thing. The rules are precisely the same, no matter how the genotype is put together. Populations must have an intrinsic rate of increase greater than zero in order to persist (see below). They must be supplied with essential resources at a sufficient rate to allow this multiplication rate to be expressed. Transgenic individuals are exposed to predators, parasites, diseases, and competitors, and suffer the same kinds of losses during dispersal as any other organisms. They may require mutualists for resource gathering, reproduction, defense, or dispersal. They must deal with the vagaries of changing weather and heterogeneous substrate in the same way as any other organisms."

But then Crawley continues in his reply in [79] in a way you would not expect from an independent scientist having written excellent and seminal papers on the ecology of transgenic crops:

"The trouble is, that it doesn't really mean anything. In the real world, GMOs are treated differently from other organisms. The reason they are treated differently is because governments and bureaucrats have decreed that it should be so. And why did they do this? Because of fear and uncertainty."

In **[79]**

The author of this paper's comment is rather simple: the 'real world' should still follow sturdy science, but unfortunately there is a 'false world' following clearly the scientifically wrong path on political and governmental levels and with the help of populist politicians and scientists, not at all justified by peer reviewed science. The last statement of Crawly is all the more astounding, as the same author published a still valid and often cited paper on long term aspects of environmental impact of GM crops, where he himself cannot find any difference between transgenic and non-transgenic crops related to long term survival, [83] his conclusions are interesting:

"These experiments involved GM traits (resistance to herbicides or insects) that were not expected to increase plant fitness in natural habitats. Our results do not mean that other genetic modifications could not increase weediness or invasiveness of crop plants, but they do indicate that arable crops are unlikely to survive for long outside cultivation. The ecological impact of plants with GM traits such as drought tolerance or pest resistance that might be expected to enhance performance under field conditions will need to be assessed experimentally when such plants are developed."

The author agrees that Crawley cannot generalize his conclusions about longevity of transgenic crops toward other, for example, stress-resistant transgenic traits, but one cannot ignore the fact that there are non-transgenic traits (bred e.g. with TILLING methods, sometimes enhances by radiation mutation) with the same characters as transgenic ones [84] — and more: According to Crawley's own logic transgenic crops with similar characteristics and ecological impact as the conventional ones should be excluded from any concern.

From here the step is a small one to call for a lowering of the obstacles in the regulation of transgenic crops as the PRRI has called for several times, the last time in May 2012 [85]: it is a call for the identification of LMOs that are not likely to have adverse effects:

"Consequently, enough knowledge and experience has accumulated to allow countries to formulate simplified procedures or exemptions for various categories. In fact, PRRI believes that the formulation of simplified procedures or exemptions is long overdue in many countries, which not only has seriously hampered the potential of public biotechnology research, but also reconfirms the misperception of many that there is something inherently dangerous about LMOs. PRRI therefore commends the MOP for starting an exchange of views and experiences on identification of LMOs that are not likely to have adverse effects. PRRI envisions that the information and concepts in this present paper facilitates a more in depth consideration by the Parties." **[85].**

Another proof of early disputes on the 'Genomic Misconception' is given in detail in Huttner *et al.* [86]:

*"The U.S. Department of Agriculture (USDA) and the Environmental Protection Agency (EPA) took a very different course than FDA, proposing entirely new regulatory schemes specifically targeting the use of the new genetic techniques in research. These regulatory schemes conflict with worldwide scientific consensus that rDNA techniques and rDNA-modified organisms are not inherently dangerous or unpredictable [**[74,87], [80] [88], [89], [90], [91]**]. There is no valid conceptual distinction regarding safety between modern and older genetic methods. The scientific community has found from millions of laboratory experiments and thousands of field trials that the precision of rDNA techniques actually enhances determinations of safety and risk. This confidence is not, however, reflected in EPA and USDA regulations on field research."*

A rich source of the history and dynamics of the transatlantic biosafety dispute can be downloaded at the COGEN site: A selection of the Statement of Werner Arber [75] and 5 publications dealing specifically with the 'Genomic Misconception' are cited here [82,92–95]. Interestingly enough they all are more or less agreeing with the opinion of the Miami Group on the molecular similarity between transgenesis and natural mutation. Mooney and Bernardi [74] edited all the downloadable chapters in a book still available and also downloadable from the SCOPE website.[1]

It is memorable to see, that also an official statement against the Genomic Misconception has been published in Mooney and Bernardi, signed by all co-authors, under the lead of Arber [75], see a quote above.

There are several more accounts on the history of the Cartagena Protocol dispute, but symptomatically, they are almost completely devoid of the molecular science behind the debate [96,97], nevertheless they give detailed insight in the chronology and the political fights at the surface of the delegates disputes. The same attitude of avoiding the mention of the different genomic views can be detected in the minutes of the first official Negotiations on the Cartagena Protocol on the Bahamas and later, all documented in the Earth Negotiation Bulletin [98].

By contrast, Krattiger explicitely draws attention to the Genomic Misconcption, but still comes to the conclusion in his chapter on biodiversity and biosafety, that although he considers the process focus in regulation not science based, it might still be the best compromise [99] to continue this way.

Cantley was mandated to produce a comprehensive report on the regulatory tools developed by governments for the OECD [100] see also [101,102], and not surprisingly, Cantley sums up the impact of the Cartagena Protocol in a crucial way:

The Cartagena Protocol on Biosafety is based on negotiations following on Article 19.3 of the Convention on Biological Diversity:

"The Parties shall consider the need for and modalities of a protocol setting out appropriate procedures, including, in particular, advance informed agreement, in the field of the safe transfer, handling and use of any living modified organism resulting from biotechnology that may have adverse effect on the conservation and sustainable use of biological diversity."

The Protocol is thus intended to protect biological diversity and human health from the potential risks arising from GMOs by providing a clear legal framework for their transboundary movement. The Advance Informed Agreement (AIA) procedure established by the Protocol will ensure that countries can make informed decisions on whether to import GMOs intended for introduction into the environment. Shipments of GMO commodities will have to fulfil specific documentation requirements.

The Protocol has enjoyed a high profile, and Environment Ministries see it as a significant instrument, in some degree a riposte to the world trade agreements; although scientifically, it is not clear that GMOs as so far developed and used in fact constitute a threat to biological diversity.

As at October 2006, 134 countries had ratified the Protocol, including the European Union; but with notable absentees, such as the United States, Canada, Argentina, and Australia — all significant agricultural exporters. New Zealand ratified, somewhat hesitantly, to exert influence to prevent the requirements imposed becoming more adverse." ***[100].***

Unfortunately, the dynamics of life DNA processes (and so many other facts in molecular sciences as described, for example, by Werner Arber were not taken properly into account when the Cartagena protocol on biosafety was conceived — no surprise when you realize how few knowledgeable molecular scientists have actively participated in the legislative process. There was only a minimal overlap of 12 experts between the Cartagena Protocol Roster of Experts and the Number of members of the International Society of Biosafety Research in 2004.[2] This means, as it has been stated by many molecular scientists that the Cartagena Protocol debates were clearly dominated by politics. It is unfortunate, that UNIDO as a United Nations Agency for Industrial Development paints, in ignoring the background of the Genomic Misconception, but also points at the political elements in the wrong and calls for revision of regulation [164], but see also the UNIDO presentation at a Kuala Lumpur Cartagena Protocol Meeting in 2007, where Tzotzos explicitly criticises event-based regulation: [165].

It also has to be stated, that proof is available that the roster of scientific experts remained practically inactive, and it is only known through the initiative of PRRI that renewal and activation of this panel would be urgently needed. See the letter of PRRI to officials of the CBD,[3] some citations:

"The Public Research and Regulation Initiative (PRRI) ***believes that the mechanism of the Roster of Experts hasn't worked to date,*** *because there is clearly no common view as to what constitutes an expert and because there is insufficient information on the BCH about the area*

[1] SCOPE website: http://www.scopenvironment.org/downloadpubs/scope44/.

[2] Roster of Experts Cartagena Protocol to ISBR: http://www.ask-force.org/web/PublicSector-Danforth-20050304/CP-Experts-Overlap-to-ISBR-2004.pdf.

[3] Letter of PRRI to CBD on expert panel activity: http://www.ask-force.org/web/PRRI-Experts/PRRI-submisison-CP-Roster-Experts-20061121.pdf.

of expertise of the experts involved. We therefore welcome the decision by the MOP to develop draft criteria, minimum requirements and to explore a quality control mechanism for experts to be included in the Roster of Experts of the BCH." ***And:***

"The types of expertise that may be needed to assist a country in meeting its obligations under the Protocol are very diverse and include scientific expertise, legal expertise, and administrative expertise. Even within these areas there are many different specialised fields, such as molecular biology, plant physiology, and population ecology. What is of crucial importance to the functioning of the Roster is that the area of expertise is explained in sufficient detail."

Sadly, the PRRI press release 2010 at the occasion of MOP5 at the Nagoya conference of the Cartagena Protocol demonstrates that practically zero progress has been made in this important issue from 2006 to 2011.[4] No wonder, that the Genomic Misconception has never been debated seriously in these circles. It also gives proof once more, that the organization of the United Nations Biodiversity Convention is not really caring enough about correct science to be implemented in this so crucial biosafety protocol. Citation from this 2010 PRRI letter:

"Tens of thousands of biotechnology researchers in thousands of public research institutes in developing and developed countries strive towards alleviating poverty, sustainable agricultural production, assuring food safety and quality and conservation of the environment. However, these same public sector scientists express concern that these efforts will be futile if regulations such as the Cartagena Protocol are not implemented in a balanced and science-based manner. They call on the negotiating Parties at MOP5 to constantly assess how the implementation of the Protocol will affect crucially important public research, to ensure that the Protocol will indeed contribute to sharing the benefits of this technology."

See the Article 19 of the Convention of the Biological Diversity, which is the root of the Cartagena Protocol [76]

Article 19 of the CBD: Handling of Biotechnology' and Distribution of its Benefits

1. *Each Contracting Party shall take legislative, administrative or policy measures, as appropriate,* ***to provide for the effective participation in biotechnological research activities*** *by those Contracting Parties, especially developing countries, which provide the genetic resources for such research, and where feasible in such Contracting Parties.*
2. *Each Contracting Party shall take all practicable measures to promote and advance priority access on a fair and equitable basis by Contracting Parties, especially developing countries, to the results and benefits arising from biotechnologies based upon genetic resources provided by those Contracting Parties. Such access shall be on mutually agreed terms.*
3. *The Parties shall consider the need for and modalities of a protocol setting out appropriate procedures, including, in particular, advance informed agreement, in the field of the safe transfer, handling and use of any living modified organism resulting from biotechnology that may have adverse effect on the conservation and sustainable use of biological diversity.*
4. *Each Contracting Party shall, directly or by requiring any natural or legal person under its jurisdiction providing the organisms referred to in paragraph 3 above, provide any available information about the use and safety regulations required by that Contracting Party in handling such organisms, as well as any available information on the potential adverse impact of the specific organisms concerned to the Contracting Party into which those organisms are to be introduced.* [76]

There is also blatant inertia visible in GE crop approval processes, and the CP organization demonstrates the usual incapability of reacting expediently enough to the growing speed of scientific innovation: a plethora of new genomic manipulations are manifested with hundreds of publications, but the biosafety research community still remains in the realms of Bt crops and herbicide tolerant crops. Correcting the legislation by following insights in the falsehood of the Genetic Misconception would also free the regulatory community from adhering to all the new kinds of gene splicing (after proper testing and analyzing), and could instead concentrate pragmatically and scientifically fully justified on *product oriented regulation*. Just two examples of innovation in transgenesis growing rapidly as a whole:

1. Zink finger enzyme assisted targeted insertion of transgenes in complex organisms [103,104]
2. The new TALES method is capable of generating site-specific DNS Breaks and has great potential for site-specific genome modification in plants and eukaryotes in general [105–107]

Alone these two gene transfer methods, much more precise and easy to use, call ultimately for a thorough revision of the regulatory process.

In a recent publication, Fedoroff *et al.* [108] deplore the US Environmental Protection Agencies (EPAs) departure from the US regulatory system toward a European approach, reacting to new EPA regulatory policies:

"Based on initial reviews of that draft proposal and recent EPA actions associated with biotechnology-derived crops, it is clear that the EPA is departing from a science-based regulatory process, instead walking down a path toward a policy based on the controversial European 'precautionary principle' that goes beyond codifying data requirements for substances regulated as PIPs (Plant Incorporated Pesticides) for the past 15 years. While this principle is politically popular in some constituencies, it is not supported by experience gained over the past several decades with transgenic crops."

And:

"Over the last two decades, advances in sequencing and genomic analysis have revealed that biotechnology is more precise and less disruptive to the genome than traditional

[4] PRRI letters Roster of Experts 2006 and 2010: http://www.ask-force.org/web/PRRI-Experts/PRRI-submisison-CP-Roster-Experts-20061121.pdf and http://www.ask-force.org/web/PRRI-Experts/PRRI-submission-CP-Roster-Experts-20101013.pdf.

plant breeding. In fact, recent genomic, proteomic, and metabolomic comparisons of varieties bred (using conventional and transgenic methods) demonstrate that transgenic plants with incorporated novel traits more closely resemble the parental variety than do new varieties of the same crop plant produced by more traditional breeding or mutagenesis techniques. These findings support the crop-level observations that transgene insertion is not inherently disruptive and that transgenic crops present no new or greater hazards than crops produced by breeding techniques now considered conventional. Indeed, they are not only less disruptive, but far more precise because they introduce or modify the sequence or expression of well-characterized genes in predictable ways, objectives which cannot be achieved by any previous method." **[108]**

Conclusions

The conclusions are crystal clear: European regulation and worldwide legislation of GM crop biosafety regulation within the Cartagena Protocol need a thorough overhaul, *a shift from process oriented to product oriented regulation* [109–112].

There can be no doubt that *product-based regulatory approaches* are closest to the scientific principle and that biotechnology is not inherently more risky than other technologies, principles, which have a long and accepted history of application in agriculture and food production, it is also less prescriptive than process-based systems, see McLean *et al.* [113].

Another valid paper showing constructive conclusions out of the regulatory conflict has been published by Cantley [101]. This text cries for action, including a roadmap for solutions, Cantley has searched for proposals with a good mixture of pragmatism and uncompromised application of present day scientific insight:

"The case for benign neglect of biotechnology has been largely lost in Europe at present, but the current Commission strategy may slowly correct this. Europe has supported research, while burdening the technology with disproportionate legislation; preaching the gospel of competitiveness, but forgetting that precautionary regulation should be dynamic and adaptive to scientific evidence and experience. As resources (scientific, administrative and political) are always limited, devoting more to small or non-existent risks subtracts them from more serious needs, thus actually increasing risks." **[101]**

A summary of the thoughts of Miller and Conko [114], p. 223ff on six strategies for reforming regulatory abuses fits best into what needs to be done:

- *Scientists must actively protest unscientific policies and Regulation*
- *Scientific institutions must stimulate public discourse*
- *The media must discount bogus science*
- *The biotech industry must advocate scientific regulatory policies*
- *All stakeholders should promote science-based public policy*
- *Rethink the government's monopoly over regulation* [114]

As long as the scientific principles of regulations are respected, the rules of internationally agreed risk assessment should be handled flexibly, according to the growing amount of positive experience, Miller [115].

- *"The degree of regulatory scrutiny should be commensurate with the perceived level of risk.*
- *Similar things should be regulated in a similar way.*
- *If the scope of regulation — i.e. the regulatory net or the trigger that captures field trials or the finished product for review — is unscientific, then the entire approach is unscientific."*

This paper of Miller [115] has been published in a volume of a study week held at the Vatican in May 2009 on invitation of the Pontifical Academy of Sciences which is also published on the website of the Vatican as an open source conference volume [116].

In the same volume, Arber came for the assessment of long term risks to the same conclusion [117]:

"Available scientific knowledge and potent investigation methodology represent an efficient and effective basis for a priori responsibly carried out technology assessments before GM organisms, either as produced by genetic engineering or as selected by classical breeding, become released into the environment. Any decision taken on such releases should be based on the specific biological functions involved, not on the ways by which the selected organisms were produced" **[117].**

It is time to move on and call for a serious amendment of national and international legislation in biosafety assessment of GM crops, as stated with uncompromising demands by [118]:

"The politicization of the regulatory process is an extremely significant impediment to use of biotechnology by public institutions for public goods. Costs, time and complexity of product introduction are severely and negatively affected (without such political impediment the technology is very appropriate for adoption by developing country scientists and farmers: it does not require intensive capitalization). The regulatory process in place is bureaucratic and unwarranted by the science: despite rigorous investigation over more than a decade of the commercial use of genetically engineered (GE) plants, no substantiated environmental or health risks have been noted. Opposition to biotechnology in agriculture is usually ideological. The huge potential of plant biotechnology to produce more and more nutritive food for the poor will be lost, if GE-regulation is not changed from being driven by 'extreme precaution' principles to being driven by 'science-based' principles. Changing societal attitudes, including the regulatory processes involved, is extremely important if we are to save biotechnology, in its broadest applications, for the poor, so that public institutions in developing as well as industrialized countries, can harness its power for good." **[118]**

And a closing word by Miller on the squandered opportunity of the Golden Rice [119] and a last chance to fulfill its great promise:

"In spite of its vast potential to benefit humanity — and negligible likelihood of harm to human health or the environment — Golden Rice remains hung up in regulatory red tape with no end in sight. In a July commentary in Nature, Potrykus pointed out that Golden Rice has been 'stalled at the development stages for more than ten years

by the working conditions and requirements demanded by regulations.'"

Recently, this view is supported by more publications:

Ingo Potrykus is calling for a revolutionized regulation of GM crops — he waits for more than a decade that his Golden Rice comes into agricultural use, but in vain. The table on the retarded history of its introduction in Nature [111] on p. 561 speaks for itself. This is particularly tragic in view of a well structured introductory organization, see http://www.goldenrice.org. Today, hundreds of thousands of children are still suffering severely under Vitamin A deficiency and connected blindness and death [120–122].

An additional recent comment is coming from Patrick Moore, former Greenpeace founder, now active for http://www.greenspirit.org [123]:

"It is a crime against humanity because some NGOs are preventing the curing of people who are dying by the hundreds of thousands a year due to vitamin A deficiency."

In Ingo Potrykus' own words: Unjustified and impractical legal requirements are stopping genetically engineered crops from saving millions from starvation and malnutrition.

Giddings *et al.* in Nature Biotechnology call for galvanizing plant science in Europe will depend on an overhaul of GM crop regulation: They call for a revision of GM crop regulation, in particular in Europe and also in the United Nation Cartagena Protocol on Biosafety [109]. Galvanizing plant science in Europe will depend on an overhaul of the tangle of indefensible regulations themselves, not on the advent of new plant breeding technologies that may escape existing rules. The world has seldom seen a greater discrepancy between the inherent hazard of a product and the level of regulatory burden imposed on it than exists today for crops improved through biotech. It is important, here, to be very clear: **There is no basis in science for regulation specific to crops and foods improved through biotech or 'GMOs'**.

This view is supported by an editorial of Andy Marshall in the same volume of Nature Biotechnology [124] with the telling headline: 'Agnostic in Agriculture'. He also calls directly for averting a global food crisis which will require the *deconstruction of several hurdles* to the deployment of new strategies in plant breeding.

There should be no illusion: the numerous risk assessment researchers and regulators on national and international levels will need to reverse some dogmatic views about biosafety of GM crops and try to learn that transgenic and conventional crops do not basically differ in food and environmental safety — this is a process which will take years, but needs to be started without further delay.

We want to close with an optimistic outlook: Pamela Ronald explains the efficiency and precision of genetic engineering in plant breeding [125]: She leaves no doubt that this technology will be an important part of sustainable agriculture:

*"Despite the demonstrated importance of genetically improved seed, there are still agricultural problems that cannot be solved by improved seed alone, even in combination with innovative farming practices. A premise basic to almost every agricultural system (conventional, organic, and everything in between) is that seed can take us only so far. Ecologically based farming practices used to cultivate the seed, as well as other technological changes and modified government policies, clearly are also required." **[125].***

Another optimistic outlook shall close the text, it comes from Swedish colleagues led by Fagerstroem [126], more details in the long Swedish text [127]:

"Risk research on GM crops in Europe has to come to an end, as do futile battles about disasters that will not happen. A dead parrot is a dead parrot, both in Monty Python sketches and in science. The way to sustainable and productive agriculture is not by maintaining expensive, parallel production systems, using different sets of crop varieties, and relying on expensive regulations for their coexistence. Instead, agricultural systems should use the best available technology at all stages, including plant breeding. It is clear that the approval and decision process within the EU for GM crops is not science-based. **The risk assessment and approval process, where the outcome is dominated by the opinions of a few self-interested stakeholder organizations with special interests is unique. It is alarming that decision-making bodies kow-tow to this non-science-based paradigm."** ***[126]***

The title of the last piece above is excellent: **Stop worrying; start growing**. Risk research on GM crops is a dead parrot: it is time to start reaping the benefits of GM

Possible solution: the Canadian regulatory system with future amendments

There is no reason to re-invent the wheel, for reasonable risk assessment strategies we better have a close look at the Canadian process-agnostic approach, focusing on the novelty of products among the new crops, a comprehensive review paper on Canadian regulation of GE crops comes from Smyth and McHughen [128]

The advent of genetically modified crops in the late 1980s triggered a regulatory response to the relatively new field of plant genetic engineering. Over a 7-year period, a new regulatory framework was created, based on scientific principles that focused on risk mitigation. The process was transparent and deliberately sought the input of those involved in crop development from non-governmental organizations, industry, academia and federal research laboratories. The resulting regulations have now been in place for over a decade, and the resilience of the risk-mitigating regulations is evident as there has been no documented case of damage to either environment or human health. ***[128]***

Those who want to know more about new technologies can read Lusser et al. for a comprehensive overview: [166]. The paper is nolens volens demonstrating the un-surmountable difficulties in regulating with a restrictive focus to transgenesis processes instead of looking at the products.

The two authors describe in detail how Canadian regulators deal with an assessment system fully taking care of the hurdles, when you leave the simplistic path of focusing on the process of transgenesis: The fully science based and still pragmatic regulatory system is now

for over a decade in place with uncontested success (this has not been the case in the mid and late nineties in Canada, read about the regulatory difficulties described by [129,130] in detail!):

Clearly, the product oriented regulation brings along a major change, including the difficulty as conventional crops have to be taken into account. The challenge was now to find a pragmatic way to avoid that all new crops have to undergo expensive and laborious risk assessment. Canadian regulators have found solutions: They based regulations on the end product that is established, not the process used to create the product. They developed over a seven years period a new classification of plants by creating a new regulatory system focusing of 'Plants with Novel Traits' (PNTs), the heart of a process — an agnostic decision making system which is now in place successfully since a decade. The process is transparent and deliberately sought the input of those involved in crop development from non-governmental organizations, industry, academia and federal research laboratories. These plants selected for closer regulation are classified as PNTs, they are modified either via genetic engineering or mutagenesis, in addition these PNTs also those that do *not* have a history of production and safe consumption in Canada: The procedure is described in detail in the Directive Dir2000-07: Conducting Confined Research Field Trials of Plant with Novel Traits in Canada, published by the Canadian Food Inspection Agency [131]. Before any experimental field release, the Canadian authorities are carefully evaluating environmental safety with the following steps, details see Directive 94-08 Assessment Criteria for Determining Environmental Safety of Plants With Novel Traits by the Canadian Food Inspection Agency [132]. The novelty and automatically the details of modern transgenic crop breeding is described with great precision [140], which is lacking in any other international regulatory legislation.

1. *''The potential of the plant to become a weed or to be invasive of natural habitats.*
2. *The potential for gene flow to wild relatives.*
3. *The potential for a plant to become a plant pest.*
4. *The potential impact of a plant or its gene products on non-target species.*
5. *The potential impact on biodiversity''* [132]

And related to the herbicide tolerant canola crops:

''Because of the above definition and the subsequent assessment categories, every herbicide-tolerant variety application that the CFIA receives is treated as a PNT, regardless of the technology used to create the herbicide-tolerant variety. Although there are very few crop varieties approved with stacked traits (corn, cotton and potato), a herbicide-tolerant variety that has additional traits stacked with it, such as drought tolerance, would be given consideration for variety approval under the following CFIA directives.

1. *Directive 94-08* [132]*: Assessment Criteria for Determining Environmental Safety of Plants with Novel Traits.*
2. *Directive 95-03* [134]*: Guidelines for the Assessment of Novel Feeds: Plant Sources.*
3. *Directive D-96-13* [135]*: Import Permit Requirements for Plants with Novel Traits, and their Products.*
4. *Directive 2000-07* [131]*: Guidelines for the Environmental Release of Plants with Novel Traits within Confined Field Trials in Canada.*

Using these directives, the CFIA assesses all PNT variety applications for environmental release and use as animal feed. It is no longer possible to obtain split approval for a crop variety in Canada, where the crop would be approved for use as animal feed but not human consumption. Figure 2 provides a flowchart of the CFIA's regulatory process. In Stage 1 of the development of a new PNT variety that is intended for unconfined environmental release and/or use as a livestock feed, the plants are required to be grown in a contained facility (i.e. glasshouse or laboratory growth chamber). Growing conditions in these types of facility follow biosafety guidelines that have been established by Health Canada and the Medical Research Council. Research institutions may develop and require that codes of practice be followed in addition to the above." ***[128]***

However, some rDNA developed plants are not PNTs, which creates some confusion for crop developers. This differs from the US regulatory system. Most jurisdictions trigger regulatory scrutiny for every new rDNA insertion into a plant's genome, but the Canadian CFIA triggers regulatory scrutiny *only* when a plant acquires a new trait, even if it is not a product of rDNA. Plants developed using traditional breeding, not rDNA, have occasionally triggered regulatory review for expressing novel traits, as in a recent case a bred barley trait with low phytate levels. [136,137]. Decades ago the zero-erucic acid oilseed rape, a clear PNT according to modern definition, would be subject to regulation today — a breakthrough in the sixties for oilseed rape as feed [138]. In the introductory phase it caused some concern about deer overfeeding with the new variety, but obviously the animals adapted soon [139].

Fig. 1 explains the first procedures in detail [128].

Unlike the Canadian Food Inspection Agency (CFIA) the Canadian Health agency is testing all transgenic products with focus on processes [141]

- *''Foods resulting from a process not previously used for food.*
- *Products that do not have a history of safe use as a food.*
- *Foods that have been modified by genetic manipulation, also known as genetically modified foods, GM foods, genetically engineered foods or biotechnology-derived foods.''*

A clear downside of the Canadian regulatory system is lacking harmonization between the three agencies involved in the decision

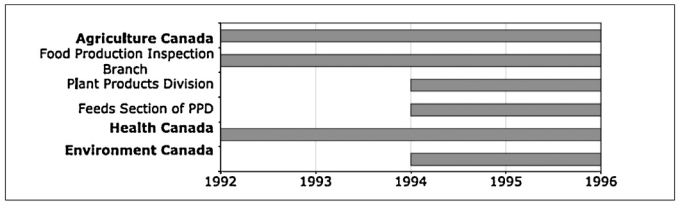

FIGURE 1

Regulatory actors involved in the development of regulations for plants with novel traits. The 7-year process of developing the regulations for PNT crops was time consuming; however, the process was scientifically justified and successful, as there have been no documented problems resulting from 12 years of commercial PNT crop production in Canada. For more information about the Canadian regulatory process see http://www.ask-force.org/web/NewBiotech/Smyth-McHughes-Excerpt-Details-Regulatory-Process-Canada-2008.pdf.

making process: Canadian Food Inspection Agency, Canady Health and Canada Environment. Canada Health also has established directives for environmental safety assessment of GMOs, but harmonization with the Canadian Food Inspection Agency is still under way and delayed and the websites from 2007 are no more found with active links as cited in [128], there are more details commented there (Figs 2 and 3).

It is interesting to note that the Canadian regulatory system respects properly done approval processes from other countries. The definition of scientific criteria for the assessment of risks of PNTs needs to be improved. However, non-novel GM crops have to undergo regulatory scrutiny also in Canada, and Smyth and McHughen would certainly support the letter petitions of PRRI to the Cartagena Protocol organization for a limited exemption of well known and well regulated GM crops [6,85] and address this request also the Canadian regulatory organizations.

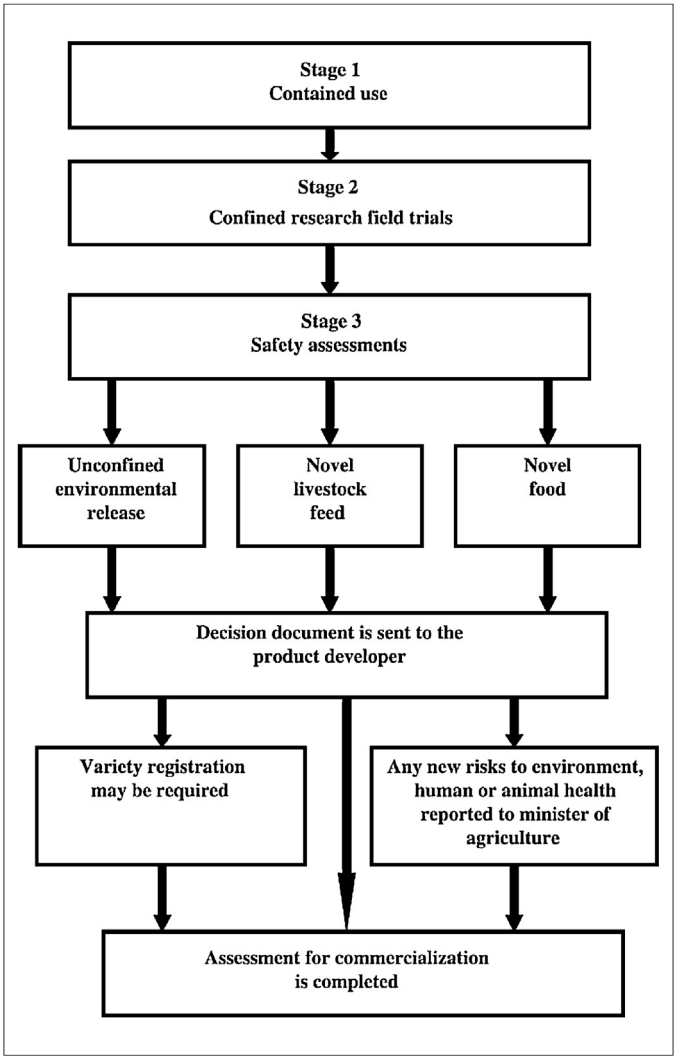

FIGURE 2

Regulation of plants with novel traits in Canada. In Stage 1 of the development of a new PNT variety that is intended for unconfined environmental release and/or use as a livestock feed, the plants are required to be grown in a contained facility (i.e. glasshouse or laboratory growth chamber). In Stage 2, the PNT variety developer must submit an application to the CFIA and receive authorization to conduct confined field trials in Canada. Directive 2000–07 is used to establish how many trials are allowed in Canada, the size of the plot and the isolation distances that are required. The safety assessment for the new variety is conducted in Stage 3. This stage is designed to address the five priority categories listed above. To provide the necessary information to satisfy these questions, the product developer is required to submit scientific data that have been gathered from the field trials.

Source: CFIA (2006), the comments from [128,141].

The time has come to re-assess the regulatory system in its scientific details, although the success in properly regulated novel traits in GM canola, soybean and maize has been considerable up to now. The comments of [128] are similar to the complaints of their European colleagues:

> *"The rigours of the regulatory requirements, in terms of the cost of conducting the studies necessary to gather sufficient data to meet the demands of the regulators for aspects such as gene flow, allergenicity and toxicity, are pushing public researchers out of the variety development industry. Public research institutions have limited budgets and simply do not have the finances to undertake the expensive research required to satisfy regulators. The concern within the seed development industry is that the commercialization of new traits will only be performed by large multinational seed developers, thereby having a potentially large negative impact on the continuing development of crop varieties that are best situated for Canada, such as canola. There is justified concern about the increase in regulatory requirements for GM crop varieties, as this increase in regulation is not justified by any increase in risk.* ***[128].***

For more details and insight it is recommendable to visit the websites of the Canadian Food Inspection Agency CFIA (http://www.inspection.gc.ca), Health Canada (http://www.hc-sc.gc.ca) and Environment Canada (http://www.ec.gc.ca) and some additional references selected [135,142–147,148,149].

One also has to realize, that the Canadian regulatory system is working smoothly up to now (some flaws described above causing unnecessary delays in approvals), not only because it sticks to product-oriented regulation, but according to [150] it maybe even more important that the agency has changed to a more entrepreneurial character within the Canadian administration, making the whole structure definitely more efficient:

> *"The CFIA has gathered together most of the Canadian government's food inspection expertise and regulatory activities. It has a workable organizational design as a departmental corporation, with elbowroom in which to innovate on the administrative and management side. A major asset of the agency is its strong core of scientific and technical employees, reinforced by multiple linkages to scientists and scientific organizations across Canada and around the world.*
> *Reinventing government is about politics as much as administration, and the present age is one of continuities as well as discontinuities in public policy and management."* ***[150].***

This pragmatic diagnosis is logically not welcome to an author like [151], who argues in a more negative way citing activists like Jeremy Rifkin, who care more about politics than science.

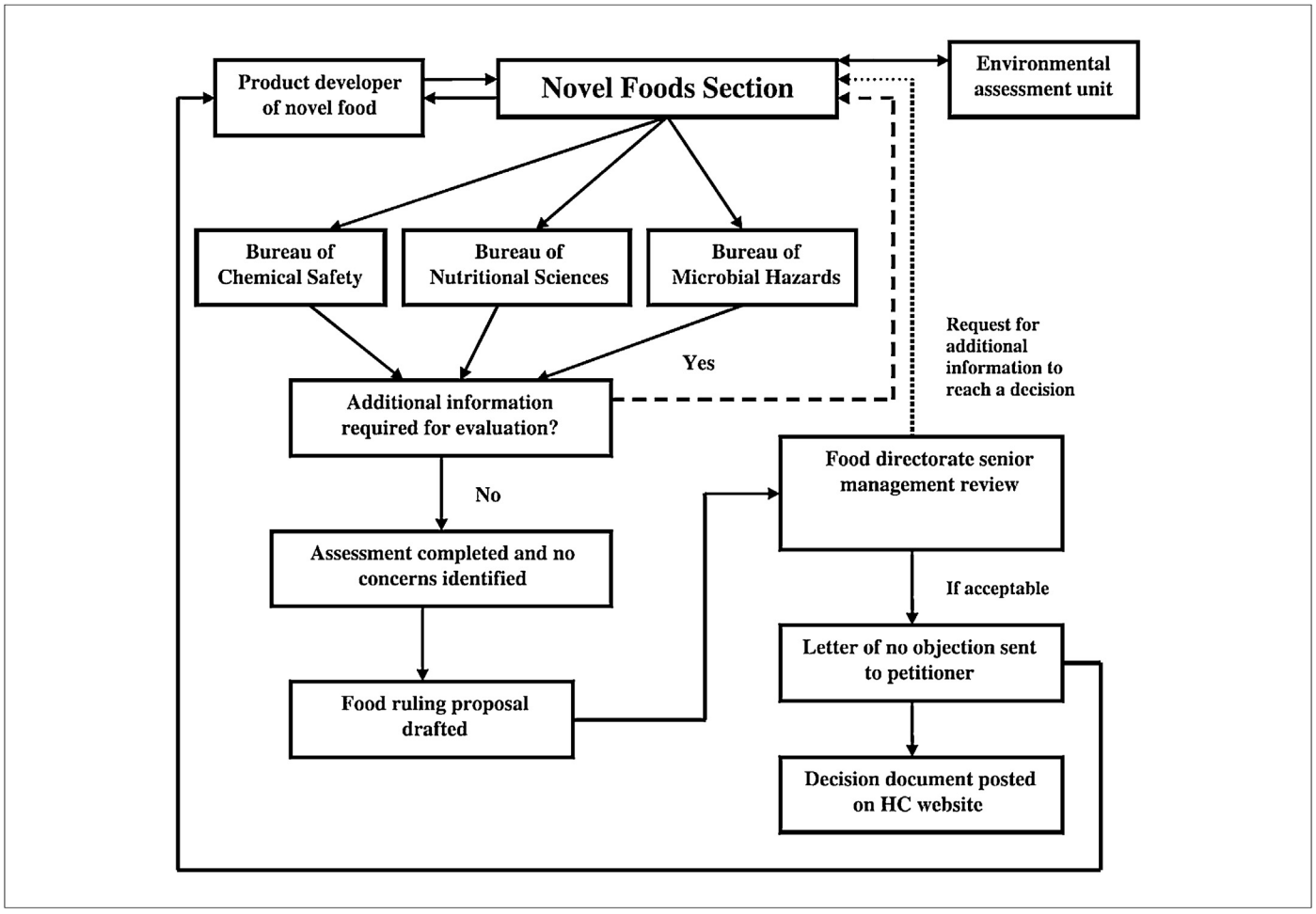

FIGURE 3

Novel food notification/submission. Regulators at Health Canada take the data from the field trials conducted by the product developer that relate to the category for novel foods in Fig. 1. This is when the nutritional, toxicity and allergenicity data are reviewed and assessed. Additional data are needed to satisfy risk assessments regarding dietary exposure, metabolization and microbiological safety. One salient feature of the Health Canada regulatory process is its use of experience from other jurisdictions. If a PNT product has a history of safe production and consumption in another country, this is admissible as data for regulatory approval in Canada. Health Canada is unique amongst the PNT regulatory bodies in this context, as the CFIA and Environment Canada will not allow a history of safe production and consumption elsewhere as admissible data. Fig. 3 provides the Health Canada regulatory process.
Source: [128,141].

There are many manifestos on re-installing science in modern agriculture from Academies and other scientific bodies, as a recent collection of Piero Morandini demonstrates [152]:

The example from the ABIC conference in Cologne 2004 [153] calls for the use of unbiased information in law-making and politics, the support of R&D to foster innovation in plant genetic engineering and the elimination of unnecessary, currently existing hurdles in laws and regulations concerning these technologies.

There should be no illusions, the search for a more science based regulatory system needs hard work for months, needs an international perspective in times of growing globalization, it may even take years to come and can only be solved with modern discursive methods of the second generation [154,155], it is also necessary to make use of proposals of regulatory innovation from people experienced in regulatory science: [156–159] and [13] to give a few examples. This debate should not be abused for a new, fancy and expensive regulatory system per see, on the contrary, what we need is a regulation in a perspective for a development of new useful agricultural products [161–163] (http://www.ask-force.org/web/NewBiotech/Chapter-5-separate-citation-numbers-not-active-2013.pdf).

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