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THE CASE FOR REGULATING INTRAGENIC GMOS

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ABSTRACT. This paper discusses the ethical and regulatory issues raised by ''intragenics'' – organisms that have been genetically modified using gene technologies, but that do not contain DNA from another species. Considering the rapid development of knowledge about gene regulation and genomics, we anticipate rapid advances in intragenic methods. Of regulatory systems developed to govern genetically modified organisms (GMOs) in North America, Europe, Australia, and New Zealand, the Australian system stands out in explicitly excluding intragenics from regulation. European systems are also under pressure to exclude intragenics from regulation. We evaluate recent arguments that intragenics are safer and more morally acceptable than transgenic organisms, and more acceptable to the public, which might be thought to justify a lower standard of regulation. We argue that the exemption of intragenics from regulation is not justified, and that there may be significant environmental risks associated with them. We conclude that intragenics should be subject to the same standard of regulation as other GMOs.

KEY WORDS: consumers, environment, ethics, genetically modified organisms, intragenics, nature, regulation, safety

1. INTRODUCTION

Modern gene technologies give scientists the power to move and/or modify specific genetic elements both within and between species.[1] ''Transgenics'' – organisms that contain genetic material from other species – represent the archetype of genetic modification; they reflect the power of modern scientists to re-engineer living organisms without regard for ''natural'' species boundaries. The violation of species boundaries has tended to feature prominently in public concern about genetically modified organisms (GMOs) (Brown and Michael, 2001; Cormick, 2003). An important recent response to this concern

[1] By ''modern gene technologies'' here we mean both recombinant DNA and RNA technologies that allow the manipulation of specific sequences of an organism's genetic material in the laboratory. Following others in this debate (Nielsen, 2003; Myskja, 2006; Schouten et al., 2006a, b), we have excluded techniques such as chemical and irradiative mutagenesis, cell-based techniques such as protoplast fusion, and traditional breeding from our definition of gene technology.

has been to advocate the use of recombinant DNA technology to produce genetic modifications without the transfer of DNA between species (Nielsen, 2003; Myskja, 2006; Jacobsen and Schouten, 2007). Organisms that have been genetically modified via modern gene technology using only endogenous genetic sequences or sequences from sexually compatible species are known as "intragenics."[2] Nielsen (2003) and Myskja (2006) have argued that the development of intragenics represents an approach to genetic modification that is more "natural" than the creation of transgenic organisms and consequently involves lower levels of risk and uncertainty. Intragenic organisms may also be significantly more acceptable to the public. This promise and new developments in science, including genomics and interference RNA technology, may lead to intragenic modification becoming a widely used approach to creating new organisms (O'Neill, 2004; Rommens, 2004; Conner and Jacobs, 2006).

Over the last three decades, many nations have developed regulatory systems designed to manage the risks of GMOs and to respond to public concern about them. In this paper, we examine regulatory systems in the US, Canada, Europe, Australia, and New Zealand. New Zealand is the only jurisdiction that explicitly categorizes intragenics as GMOs. Canadian regulations, which focus on the products of gene technology and their characteristics, rather than the process whereby they have been created, capture intragenics in their regulation of GMOs. The United States has a similarly product-focused, but less precautionary approach wherein intragenics are treated in the same way as other GMOs – which is to say that they are not subject to any dedicated regulatory attention. In Australia, intragenics lie entirely outside the scope of GMO deliberate release regulations; research dealings with intragenics may also go unregulated. In Europe, intragenics are probably captured by GMO regulations, depending on their interpretation, but this may change as a result of industry pressure and arguments from scientists and philosophers.

If intragenics are the way of the future for genetic modification, it is timely to revisit the debate about the classification of novel organisms, to ensure that any decisions about the classification and regulation of intragenics are well-founded. We critically evaluate the arguments that have been made in favor of intragenics over transgenics and argue that these are insufficient to justify a lower standard of regulation of intragenics. There may be significant risks

[2] Such organisms have also been described elsewhere as "cisgenics" (Schouten et al., 2006a; Jacobsen and Schouten, 2007) and "autotransgenics" (Nam et al., 2001). We have chosen to follow Nielsen (2003) in using the term, "intragenics," which includes but is not restricted to these other categories where they are more strictly defined (for example, we do not use the restriction introduced by Jacobsen and Schouten (2007) that native DNA sequences are necessarily accompanied by their native promoters in intragenics).

associated with intragenics and other classes of GMO that may not be adequately regulated by existing schemes. We conclude that intragenics should be subject to the same standard of regulation as transgenic organisms.

2. INTRAGENICS: PAST, PRESENT, AND FUTURE

Intragenics are organisms created using modern gene technology, including the deletion or silencing of genes within an organism (endogenous genes), the "up-regulation" or "down-regulation" of endogenous genes, and the introduction of genetic elements from different varieties or strains of the same species or of related, sexually compatible species.[3] These technologies make possible a range of novel genotypic and phenotypic changes not possible via traditional or modern (cell-based introgression and mutagenesis) breeding techniques. As well as eliminating the linkage drag that complicates the introduction of new genes via breeding, recombinant techniques allow characterized traits to be introduced directly without requirement for selection (of the trait), increasing the range of possible modifications. Intragenic organisms have played an important part in the history of modern biotechnology, with some of the most (in)famous GMOs being, in fact, intragenic creations. In this section, we will briefly discuss a number of examples of intragenic organisms from the past, present, and likely future of biotechnology, in order to provide a historical and scientific context for our investigation of the issues raised by intragenic organisms.

2.1. *"Ice minus" Bacteria*

The first "genetically modified organism" to be field tested was an intragenic. It was a strain of bacteria known as "ice minus," which was released in the US in 1987 (Krimsky, 1991, Chapter 7). This strain of *Pseudomonas syringae* was a deletion mutant in which a gene associated with ice nucleation was deleted (Rhein, 1985). The wild-type (normal) strain of this bacterium colonizes plants and stimulates ice formation by expressing a protein on its surface that causes ice to form at temperatures as high as 1.5°C. It is this ice formation, rather than the low temperature itself, that causes frost damage in plants. The deletion mutant, in which the gene for this protein

[3] Note that techniques for gene silencing, including the powerful new technology of interference RNA, may require the insertion of "antisense" genetic sequences, i.e., sequences in reverse orientation. It is unclear whether the national regulatory regimes we survey below would regard these sequences as "foreign" or "synthetic" and whether they would affect the status of a modified organism as intragenic or transgenic. Given that these sequences do not code for protein in the modified organism, but regulate endogenous gene expression by the action of nucleic acid molecules, it seems likely that they will be regarded as intragenic. We certainly regard them as such.

has been removed, can out-compete the wild type in crop situations and thereby protect crops from frost damage (Orser et al., 1984). The first experiments to generate an ice minus bacterial strain made use of chemical mutagenesis to give rise to the desired deletion. However, the experiments were subsequently improved upon using gene technology to produce a more stable, genetically defined bacterium (Krimsky, 1991, Chapter 7), rendering the bacterium an intragenic organism.

2.2. *''NoGall'' Agrobacterium radiobacter*

In 1987 the Australian Genetic Manipulation Advisory Committee (GMAC) received an application from the University of Adelaide for the deliberate release of a modified *Agrobacterium* strain intended to be used as a pesticide. The bacteria, which were labeled ''NoGall'' for commercial purposes, were a strain of *Agrobacterium radiobacter*, a bacterium that infects plants and causes crown gall disease, a cancer-like disease that results from the transfer of genetic elements from the bacterium into cells of the plant stem. Because of this transfer capacity, *Agrobacterium* is also used widely to introduce recombinant DNA into plant cells in the laboratory. The new strain, K1026, was an improved version of a previously discovered strain of non-pathogenic *Agrobacterium* that produced an antibiotic effective against pathogenic crown gall-causing agrobacteria. The previous strain had been only partially effective because the antibiotic genes were located on a plasmid that could be transferred to the pathogenic strains and this transfer gradually conferred immunity to the antibiotic. In the improved strain, genetic elements in the plasmid allowing it to be transferred were removed, alleviating the problem of resistance (Jones et al., 1988).

The NoGall strain is intragenic because it has been subject to a specific modification of its genome using recombinant DNA technology. No DNA was added (or modified), but some was removed. The ambiguous status of intragenics (are they GMOs or are they not?) is highlighted by the fact that, despite being non-transgenic, NoGall has been described as ''the world's first commercial pesticide made from a live, genetically engineered organism'' (Stephenson and Warnes, 1996) but also, in a disturbing piece of doublespeak, was referred to on a web listing of the company that commercialized it, Bio-care Technology Pty Ltd, as a ''generically manipulated (sic) bacterium'' (http://www.ats.business.gov.au/ats-members/nogall-control_of_crown_gal.htm, accessed 6th May, 2004).

2.3. *Giant Fish*

More examples of intragenic modifications are found in aquaculture. Over 10 years ago, salmon were genetically modified for enhanced growth using

an all-salmon genetic construct; these modified salmon achieving an 11-fold increase in size compared to normal salmon (Devlin et al., 1994). These salmon have been used extensively as model organisms to test the physiological and environmental effects and risks of growth enhancement in fish (Devlin et al. 2004). Interestingly, these earlier intragenic GMOs were referred to as transgenic, and little distinction has been made between intragenic and transgenic examples in studies of growth-enhanced fish (Hallerman et al., 2007).[4] More recently, a species of mud loach (*Misgurnus mizolepi)* has been engineered by a research group based in South-Korea to grow up to 35 times faster (and potentially much larger) than its unmodified counterparts (Nam et al., 2001). This was achieved by linking a mud loach gene expression promoter with a mud loach growth hormone. This modification is described by the researchers as an ''autotransgenic'' modification.

2.4. *Daughterless Carp*

Another example of an intragenic modification in fish that has been proposed for the future is the one envisioned in the ''Daughterless Carp'' project of the Australian Co-operative Research Centre for Pest Animal Control. The project is aimed at controlling carp in Australian waterways and thereby reducing their destructive environmental impacts. One approach that is being considered involves using gene technology to ''switch off'' a gene associated with sex development – the aromatase gene – in carp. The aromatase protein acts on carp embryos to stimulate development of females (all carp embryos are initially male). Silencing this gene by introducing a genetic element (via ''antisense DNA'') that will bind to the messenger RNA of the gene when it is ''transcribed'' and thus prevent its expression results in embryos remaining male. It is expected that release of modified carp would result in a prolonged reduction in the number of females and would therefore significantly reduce the carp population over a period of years (Davidson, 2002; Dick, 2004).

2.5. *All-native Spuds*

A number of GM plants have involved intragenic modifications. For example, the famous FlavrSavr tomato, the first GM food approved in the US in 1992, used an antisense fragment of a tomato gene (for a ripening enzyme) to produce a delayed ripening variety (Kramer et al., 1992). FlavrSavr is not, strictly speaking, an intragenic plant because it contains transgenic regulatory elements, such as antibiotic markers from bacteria and

[4] Some growth enhanced GM fish have used transgenes (for example, antifreeze gene promoters from flounder and pout) while others have these transgenes replaced by native genetic sequences.

a viral promoter. However, recent advances in intragenic technology in plants have been made by researchers at the Simplot company (Rommens, 2004). The Simplot group has found homologous sequences within plants (which they call P-DNA) that operate to effect the transfer of DNA between plant cells in the same way as the more familiar *Agrobacterium* system and have used these sequences from the plant of interest to construct new transfer plasmids. They have also identified plant-based promoters, markers, and tagging elements. Using these approaches, they have developed genetically modified potatoes that contain only potato DNA but that are resistant to stress-induced browning.

2.6. *Herbicide Tolerant Crops*

The success of the Simplot company's efforts suggests that we are likely to see more intragenic plants produced in the future. In particular, Rommens et al. (2004) have suggested the application of the techniques they have used to generate herbicide tolerant plants. Herbicide tolerance has been the dominant application of genetic modification since GM crops began to be commercialized, in part because it provides its own selection process.[5] This convenient feature of herbicide tolerance means that it can easily be pursued using other techniques, such as intragenic modification or "directed molecular evolution" (Snow, 2003), or indeed by mutagenesis and "traditional" breeding.

2.7. *Reassembling the Genes*

Our new knowledge that differences between species are more a matter of how (and which) genes are expressed rather than of which genes are present in an organism's genome (Dennis, 2002; Noble, 2006) suggests that it will eventually be possible to extensively redesign organisms by deleting, amplifying, altering the expression of, or mutating, existing genes *within* a genome using recombinant DNA technology (Jefferson, 2001; Nielsen, 2003). Researchers are already working on – and have had some success in developing – intragenic vector systems to allow modification of organisms without requiring the use of foreign DNA (Rommens, 2004; Conner and Jacobs, 2006). Powerful techniques are emerging from new understandings of gene regulation, which, together with access to vast amounts of genetic information through genomics, will allow increasing control over the phenotype of organisms without needing to introduce DNA from other species.

[5] Of course, the development of herbicide tolerant plants also allows the new variety to be linked to a proprietary chemical, thus guaranteeing sales of the chemical alongside the plant variety. This approach to genetic modification has made millions for companies such as Monsanto and Syngenta and has made a significant contribution to the public cynicism and opposition that has developed towards GM crops (Schmitz, 2001).

As gene technology advances, it may therefore become possible to replicate the phenotypes produced by many transgenic modifications using only intragenic modification.

3. INTRAGENICS AND THE REGULATION OF GMOS

A variety of regulatory systems for biotechnology have emerged around the world in the last few decades, many responding to – and all influenced by – public concerns about GMOs. In this section we examine how regulatory schemes in North America, Europe, Australia, and New Zealand classify and regulate – or fail to regulate – intragenics.

3.1. *USA*

The first application for approval for the deliberate release of a genetically modified organism in the US was for the "ice minus" bacterium, an intragenic organism. At that time, the approval process was governed by the US National Institutes of Health (NIH) through their Recombinant DNA Advisory Committee (RAC) (Krimsky, 1991). Following this high-profile case, a policy directive emanated from the White House exempting deletion products and also modifications involving "regulator genes" from review, a directive that was taken up by the RAC soon after (Piller, 1986).

The US has since relaxed regulatory requirements for biotechnology (Lehrman, 1992; Wright, 1994) and frames regulation of GMOs in terms of existing legislation. A Coordinated Framework for Regulation of Biotechnology was established in 1986, and still forms the basis for GM regulation in the US today. However, the framework merely provides a policy rationale for the use of other pieces of legislation to regulate GMOs, based on their intended use (as insecticides, foods, etc.) and on product-related hazards. The process of genetic modification is not considered to involve unique risks or require dedicated regulatory attention, beyond that required for its products. This means that various applications of GM, and various stages of the process of their development, from research through to commercial release, are regulated by different bodies. It also means that, in principle, intragenics are given the same scrutiny as transgenics by the various pieces of legislation that consider their product characteristics.

Numerous GMOs and GM products have passed through the approval process for commercialization in the US, most being granted unregulated status after petition by the company involved. These included delayed ripening tomatoes such as the FLAVRSAVR tomato, which contains an antisense gene fragment based on a tomato gene (Kramer et al., 1992). While the presence of an inserted tomato fragment would make this an

intragenic, the delayed ripening tomatoes in fact contain other transgenic elements (see Section 2.5 above). However, in determining these applications as safe, the Animal and Plant Health Inspection Service (APHIS), clearly assessed the intragenic trait as well as the transgenic elements (APHIS, 1992). It appears, therefore, that the product focus of the US system does not distinguish strongly between intragenic and transgenic GMOs in practice. However, it is also the case that the product focus does not ensure a precautionary approach to novel organisms, and the US system is therefore generally regarded as the most laissez faire of international regulatory systems for GMOs (Jasanoff, 1995). Liberal use of concepts such as ''substantial equivalence'' and ''generally regarded as safe'' has led to many new varieties and products being exempted from regulatory scrutiny on the basis of ''familiarity'' (Busch, 2002).

The low standard of regulation in the US is illustrated in the failure of the regulatory system to pick up certain classes of GMO. A transgenic ''GloFish'' designed for aquariums was commercially released in the US in 2004 without requirement for regulatory approval because it did not fit within existing legislation (Bhattacharya, 2003; Hallerman, 2004). Growth-enhanced GM fish are currently under the regulatory scrutiny of the FDA Center for Veterinary Medicine (CVM), by virtue of the growth-enhancing hormones being considered veterinary medicines. A transgenic salmon is currently being considered by the CVM (Logar and Pollock, 2005). It seems unlikely that this approach would be appropriate in the case of intragenic growth-enhanced fish in which an existing endogenous hormone is over expressed (and could therefore hardly be described as a medicine). If this is the only avenue for regulation, these intragenic fish may escape regulatory scrutiny entirely, despite the recognized environmental risks (Devlin et al. 2006).

In summary, because of the lack of dedicated regulation in the US system, and because this system concentrates on the product rather than the process of genetic modification, it does not explicitly exclude intragenics from possible regulation. However, nor does it guarantee that intragenic organisms will be subject to adequate regulatory scrutiny.

3.2. *Canada*

Canada's regulatory system also explicitly takes a product focus and is built upon existing legislation and regulatory agencies. Canada does not have dedicated regulations for GMOs; instead GM products are regulated under various agencies. The Canadian system tends to be more precautionary than the US system, however, and requires detailed assessment of GMOs through provisions of the Seed Act 1985, which require regulatory approval of all plants with new traits (PNTs) (CFIA, 2004). PNTs include new varieties produced by any

method that have traits that are not present in that species in Canada. These include but are not restricted to genetically modified plants, suggesting that intragenics, in principle, receive equal scrutiny within this system.

We could find no examples of genuine intragenics on the list of PNTs so far approved for release by the Canadian Food Inspection Agency (CFIA). However, there are examples of assessments of PNTs developed through conventional breeding or cell-based techniques, including corn varieties tolerant to herbicides (sethoxydim, imidazolinone) developed from somaclonal mutants (mutants generated in tissue culture under selection pressure).[6] The assessment of new conventionally bred varieties alongside transgenics suggests that intragenics with new traits would, in practice, also be assessed. GM salmon, both transgenic and intragenic, have not yet been proposed for commercial use in Canada, but Fisheries and Oceans Canada scientists are currently researching risks and containment measures for GM salmon, in preparation for decision-making on their introduction (Devlin et al., 2006).

3.3. *Europe*

While different European nations have taken different approaches to GM regulation, the general tendency, established by two European Union Directives and their amendments, has been to single out GMOs as a distinct category of organisms on the basis of the novel character of the process whereby they have been created and to regulate them with dedicated legislation (Jasanoff, 1995; Levidow et al., 1996; Shohet, 1996).

The definition of a GMO in the European Directive governing deliberate release of GMOs into the environment (European Parliament, 2001) is broad and apparently all encompassing, referring to any "new combinations of genetic material" that are produced by processes that "do not occur naturally." The Directive currently excludes mutagenesis and cell fusion involving sexually compatible plants, but does not exclude from regulation new combinations that involve only native genetic material, and in this sense, does not exclude intragenics. However, the Directive explicitly refers to the *insertion* of nucleic acid molecules, suggesting that intragenics formed by the deletion of genes may not be covered. Presumably, where organisms have had genes silenced by the insertion of nucleic acid materials (e.g., antisense genes, interference RNA), they would constitute "new combinations of genetic material."

Those organisms assessed in the EU that are closest to intragenics include a delayed ripening tomato developed by Zeneca, and a potato containing a modified ratio of starches. The tomato is similar to the FlavrSavr but has a partial sense gene for polygalacturonase (PG) from

[6] See Canadian Food Inspection Agency, Plant Biosafety Office, Decision Documents at http://www.inspection.gc.ca/english/plaveg/bio/dde.shtml (accessed 9 Jan 07)

tomato inserted into it, which results in partial gene silencing. The modified tomato and potato lines were assessed by the Scientific Committee on Plants in 1998 and as such seem to have been judged like any other. However, once again, both lines contain a number of transgenic regulatory elements, for example, the GM tomato contains the cauliflower mosaic virus promoter. Much of the risk assessment by the Committee focused on antibiotic resistance genes and other transgenic elements and their potential for transfer (EU SCP, 1998). It is, therefore, difficult to make conclusions from these assessments about the specific regulation of intragenics in the EU.

Schouten et al. (2006b) suggest that the European regulations will, by and large, include intragenics. However, Schouten et al., as well as a number of other European authors have called for a revision of the status of intragenics (Nielsen, 2003; Myskja, 2004, 2006; Schouten et al., 2006a, b; Jacobsen and Schouten, 2007). Moreover, as we discuss further below, there are significant institutional pressures pushing towards a lower standard of regulation of intragenics in contradistinction to transgenics. We believe that it would be naive to rely on intragenics continuing to be regulated alongside transgenics in Europe in the absence of explicit attention being paid to their status.

3.4. *Australia*

After a lengthy period of political inertia over the GM issue, during which a voluntary system based on the Genetic Manipulation Advisory Committee monitored deliberate releases of GMOs, the Australian Government finally passed the Gene Technology Act in 2000, which established a Gene Technology Regulator with statutory control over dealings with GMOs. The Act defines gene technology as "any technique for the modification of genes or other genetic material" not including sexual reproduction, homologous recombination, or techniques specified in the Regulations (Gene Technology Act, 2000, Section 10). The Regulations can declare organisms, or classes of organisms, to be genetically modified or not for the purposes of the Act, and also "exempt" or not. The Gene Technology Regulations 2001 state that organisms that are not GMOs include "a mutant organism in which the mutational event did not involve the introduction of any foreign nucleic acid (that is, non-homologous DNA, usually from another species)" (Schedule 1, Part 1, Item 1).[7] In a recent review, a decision was made to keep the current definitions (Timbs et al., 2006).

The discretion to exempt organisms from regulation and to employ other discretionary categorization (for example, to deem dealings "low risk") is a key feature of the Australian regulatory system and gives the Regulator considerable power in deciding which modified organisms will be scrutinized

[7] A "mutant organism" here refers to any organism which has an altered genotype.

and which will not. The distinction between ''not genetically modified'' and ''exempt'' is significant because dealings with exempt organisms can only take place in containment in accredited organizations and the exempt status remains, in theory, under review by the Regulator. Dealings with organisms declared ''not genetically modified,'' including gene technology research and deliberate release, go entirely unregulated. The extent to which deeming an organism ''not genetically modified'' removes the development and release of novel organisms from the regulatory (and public) gaze is illustrated by the history of NoGall. The application for commercial release of the product was granted approval by GMAC under the previous voluntary system of regulation in 1991 (GMAC PR-05) and as a consequence NoGall is widely used as a registered pesticide in nurseries and orchards in Australia. NoGall was not granted a deemed licence under the Gene Technology Act, however, because it was defined as not genetically modified by the Regulations. No mention is made of it on the website of the Office of the Gene Technology Regulator (OGTR), apart from an archived GMAC Public Information Sheet that is presented on the website ''for historical purposes.''

The Australian regulations, therefore, seem to exclude most intragenics. There remains some uncertainty about certain classes of intragenics, such as those containing antisense genes (is this a homologous or non-homologous sequence?). Such questions are likely to become important as the use of antisense and interference RNA techniques to modify organisms becomes more widespread. Current examples of intragenic modifications are likely to require a licence from the Regulator by virtue of the presence of transgenic sequences such as markers and promoters in the modified organism (Conner and Jacobs, 2006). However, as intragenic technology improves, any all-native GMOs that are developed (i.e., genuine intragenics) will entirely escape the Australian regulatory system. Unless they fall under some other jurisdiction (e.g., as a veterinary or agricultural chemical), there will be no restriction on the laboratory development, commercialization, or release of these GMOs.

3.5. *New Zealand*

Of the jurisdictions we have surveyed, the only one that explicitly includes intragenics in GMO regulations is New Zealand. Like the Canadian system, the NZ Hazardous Substances and New Organisms Act (HSNO, Act 1996) treats any new organism (including existing organisms that are new to the New Zealand environment) as worthy of regulatory scrutiny, regardless of the process by which it was made or introduced. However, the NZ system does take account of genetic modification as a new process and provides provisions under the Act for dealing with GMOs. These include a definition

of a GMO as "any organism in which any of the genes or other genetic material have been modified by *in vitro* techniques" (or offspring of such organisms) (Section 2, Part 1). The definition explicitly mentions organisms produced by either intra- or inter-specific gene transfer (but not by mutagenesis or breeding techniques). Both the process of intragenic modification and its products therefore receive attention from the regulator in New Zealand.

4. EVALUATING INTRAGENICS

In a recent paper published in this journal, Myskja (2006) has argued that there are good moral reasons to prefer the development and use of intragenic rather than transgenic organisms. Myskja suggests that intragenic organisms are more acceptable to the public than transgenic organisms and that this is itself a reason to prefer intragenics. Myskja furthermore suggests that the public's opinion is, to a certain extent, well founded because intragenic organisms are more "natural" than transgenic organisms and therefore do not give rise to novel risks. These purported advantages of intragenics might also serve as an argument that they should be subject to less regulatory scrutiny than transgenics, or perhaps even be exempt from regulation (Schouten et al., 2006a, b; Jacobsen and Schouten, 2007). In this section, we evaluate these claims, arguing that the case for intragenics ultimately rests on whether they do in fact address the substance of public concerns about GMOs. Furthermore, we argue that most of these concerns do not, in principle, distinguish between transgenic and intragenic manipulation and that consequently there is little ground to exempt intragenics from regulation.

4.1. *Public Opinion and Regulation*

Myskja (2004, 2006), Nielsen (2003), and Conner and Jacobs (2006, p. 195) have all noted that intragenics may be more acceptable to the public by virtue of the fact that the modifications involved respect species boundaries and therefore seem more "natural" than the production of transgenic organisms. They suggest that this in itself establishes a substantial presumption in favor of the development of intragenics and consequently in favor of intragenics being subject to a lower standard of regulation than transgenics.

It is important at this point to distinguish any possible *normative* argument for intragenics based on their greater acceptability to the public from *pragmatic* arguments for the development of intragenics that also appear in the literature (Myskja, 2006). If intragenics turn out to escape regulation by

the regulatory frameworks designed to regulate transgenic organisms, or if the public is less likely to object to the release of an intragenic organism, this establishes a clear *pragmatic* reason for researchers and/or corporations to prefer intragenics in order to reduce the likelihood that their product will fall foul of the regulator, or of public opinion. Thus, for instance, Nielsen (2003) has recommended distinguishing intragenic modifications as a distinct class of genetic manipulations in part because doing so might allow researchers and manufacturers to "extend the existing consumer familiarity with conventional products to the genetically modified counterpart" (p. 228). We suspect that the potential of intragenics to escape regulation under the existing laws and also to undercut public opposition to GMOs will lead to a great deal more interest in – and development of – intragenics in the future. However, these are not as yet *moral* reasons to prefer intragenics.

In his discussion of a possible *moral* case for intragenics based on the public's apparent preference for intragenics, Myskja (2006) fails to adequately distinguish an argument about democracy from an argument in favor of a preferred outcome in the democratic process. Whether or not the public's apparent preference for intragenics establishes a moral case for intragenics depends on whether one understands the literature on intragenics as a contribution to a debate about how (and whether) they should be regulated or – alternatively – as a set of observations about how governments, producers, and researchers should proceed once this debate has been concluded.

At one level, we agree that regulation of modified organisms should be in accordance with public opinion on the matter. Science policy should indeed ultimately be democratic. However, this is an observation about democracy and political process rather than about what policy we *should* pursue in relation to the regulation of novel organisms. Agreeing that a public policy decision should be made democratically and that researchers and corporations should respect the results of democratic decisions says nothing about what the substance of those decisions should be. The question as to whether or not the public is justified in its apparent preference for intragenic organisms is a different matter entirely. This is a question of substance, which is currently being debated within a (more or less) democratic community, rather than of process.

If we understand the literature about intragenics as a discussion of the question of substance, then the mere fact of the public's preference for intragenics counts for little. While a willingness to respect others who hold different beliefs is an important part of citizenship in a liberal democratic society, respect for persons and respect for beliefs are not the same thing. If the public has false beliefs about genetics or gene technology, these beliefs should not play any part in settling the debate about the question of substance. It is not a marker of respect to fail to challenge or engage with

beliefs you know to be false—and it is clear that several of the authors advocating the use of intragenics believe the public's preference for more "natural" organisms to reflect irrational and unfounded beliefs about the significance of the natural or the risks involved in genetic modification.

Myskja (2006) obviously senses that the real issue here is the question of substance but tries to insist that the correct resolution of this debate remains a democratic one by arguing that the public's concerns about GMOs stem from an "alternative worldview" that should not be judged to be either more true or more false than the scientific worldview preferred by other parties in the debate. However, to grant this further claim would be to embrace a sweeping relativism about empirical matters with the implication that there was *no* answer to the questions about whether or not intragenics are more "natural," or involve less risks, than transgenics and thus (putatively) to concede that scientific questions can only be settled at the level of process by embracing democracy. We say "putatively" here because it does not in fact follow – at least, not uncontroversially – that in the absence of any external truths with reference to which to settle a debate settling it democratically has any more claim to be the right way to proceed than various alternatives (for instance, settling the matter in favor of the most powerful party, in the interests of social stability).[8]

We think that it is indeed important to conduct a debate about intragenics on these questions of substance, in part precisely because a failure to do so concedes too much to critics of science and scientific method. This requires directly addressing those responses to the public's concerns about GMOs that argue that intragenics are more benign than transgenics. Indeed, even the argument that the development and use of intragenic organisms does address the public's concerns about GMOs rests on substantive claims about intragenics that deserve examination. This is the task to which we now turn.

4.2. *Intragenics and "respect for nature"*

A large part of public hostility towards GMOs arises from the conviction that transgenic organisms are "unnatural" and that scientists are "playing God" when they create novel organisms by moving DNA across species boundaries (Myskja, 2006, pp. 226–228; Lammerts Van Bueren et al., 2007, p. 405). Researchers' enthusiasm for intragenics in turn stems from the belief that intragenic modification addresses these concerns by being more natural

[8] None of this is to deny that scientists and the public are often concerned with different questions when it comes to the debate about GMOs or that the exploration of alternative ways of framing this debate is a useful and important exercise . However, it *is* to deny that the existence of alternative frameworks itself establishes a moral case for a question to be settled in a particular way without considering the substance of the issue.

and modifying life *less* than transgenic modification. Variations of this argument focus alternatively on the nature of the process of modification or the nature of its products. Myskja (2006) has argued that intragenic modification demonstrates respect for nature by confining the transfer of DNA to within species boundaries. Schouten et al. (2006b) have argued that intragenics are more natural because, in theory, they might have arisen as a result of mutation or traditional breeding.

Whether or not confining the transfer of DNA to within species boundaries renders modified organisms more "natural" depends on how we understand the relationship between genomes, species, and nature. Given that only a tiny proportion of the functional genes of any species is unique to that species and that many genes are conserved across kingdoms, the identity and integrity of a species are arguably embodied in the "order" or "structure" of its genetic material, and in patterns of gene expression, rather than in the genes themselves (Noble, 2006; Lammerts Van Bueren et al., 2007). It is, therefore, unclear whether intragenic "tweaking" represents a less profound change to a species' "identity" than the introduction of exogenous genes. Indeed, it might be argued that transformations of phenotype achieved by intragenic modification of a species' genome blur the line between species *more* than does transgenic modification by more radically disconnecting phenotype and genomic heritage; were intragenic modifications to become widespread we would no longer be able to use our knowledge of an organism's species as a reliable guide to its phenotype. Moreover, small changes do not necessarily lead to small effects, as chaos theory attests. Manipulating gene expression within an organism may result in a more significant change in phenotype than introducing foreign DNA, depending on the nature of the modification. As we discuss further below, the ecological impact of a modified organism depends on its phenotype and its environment and their interaction, rather than its origin. Intragenic organisms may, therefore, be just as "unnatural" as transgenic organisms in their character and ecological impact.

It is true that, as Schouten et al. (2006a) argue, in theory some intragenic modifications might occur in nature, through mutation or other evolutionary processes, whereas others might be capable of being produced by "traditional breeding practices."[9] The argument that because an organism might have evolved naturally it therefore should not raise especial concern involves a surreptitious reference to a belief about the importance of process. It draws on the idea that evolutionary processes operate at a pace that works to minimize catastrophic outcomes (Myskja, 2006, pp. 226–228).

[9] It is worth noting here that "traditional breeding practices" listed by Schouten et al. include practices such as mutagenesis, induced polyploidy, and cell fusion (and advances in these), which are relatively recent "traditions."

Whether this is true in any meaningful sense is a larger question than we can hope to resolve here; we must settle for highlighting the key role played by this claim in the argument for intragenics.

Regardless of whether particular modifications *might* occur naturally, it is clear in the case of deliberately created intragenic organisms that they have not. Arguments based on the presumptive virtues of organisms that are the result of natural selection are irrelevant to the assessment of these modified organisms. Scientists are still rewriting evolutionary history and creating novel organisms when they create intragenics – and thus are still "playing God." Of course, this is also true of those engaged in traditional breeding. Yet, again, intragenic modification is a far more powerful technology than traditional breeding and can be expected to achieve a wider range of more radical modifications more quickly. This is one of the reasons that researchers are so enthusiastic about the technology. As noted above, intragenics respect species boundaries only because – and to the extent that – these no longer stand in the way of researchers engineering organisms with the features they desire. The wisdom and right they assume in doing so are not lessened by the further claim that their products might also have come into existence had the natural world turned out differently.

Thus, neither Schouten et al. nor Myskja succeed in their arguments that intragenics are more "natural" than transgenics (Lammerts Van Bueren et al., 2007). It might be argued that by facilitating a radical divorce between a modified organisms' genomic heritage and its new character, intragenic modification is more corrosive of the idea of "nature" than transgenic modification.

4.3. *Modified Organisms and Novel Risks*

Another important set of public concerns about GMOs stem from fear that novel organisms may generate novel risks, in particular, risks to people who consume them and also risks to the environment. We discuss the extent to which intragenic organisms might generate these risks below. However, before proceeding to this task, we must first consider an important argument – which parallels the argument that intragenics are more natural than transgenics – that intragenics are *a priori* less likely to generate these risks by virtue of their putative similarity to existing organisms.

For scientists and regulators, the more "familiar" a GMO is, the more confidence we may have in predicting its impacts on human health and the environment. The more similar it is to existing organisms, the less likely it is to cause novel problems. For instance, Nielsen uses "genetic relatedness" (or conversely, "genetic distance") based on the taxonomic proximity of the recipient and source of introduced DNA as a proxy for "the potential for

the engineered trait to evolve spontaneously'' (Nielsen, 2003, p. 227) and, by extension, as a measure of safety. Similarly, Myskja (2006, p. 234) argues that the risks involved in the creation of intragenic strawberries are less than those that would be involved in creating transgenic strawberries because confining the movement of genetic material to within the strawberry's genome reduces the level of uncertainty involved. Schouten et al. (2006c) go so far as to suggest that, because ''cisgenics'' do not alter the gene pool of a species, cisgenic modification provides ''no novel traits.''

The OECD has discussed the concept of ''familiarity'' in the context of risk assessment of GM crops, and makes clear that (a) familiarity does not equate with safety, but provides a tool for risk assessment; and (b) that familiarity arises from similarity between organism + trait + environment combinations (OECD, 1993; Madsen et al., 2002). Yet any argument that intragenics generate fewer risks than transgenics by virtue of being more familiar is necessarily based on genetic relatedness alone. Underlying this argument is an assumption that movement of genes within a genome gives rise to a small phenotypic change. Yet the potential of intragenic modification is premised on the fact that this is not the case. Even if the deliberate manipulation of an organism's genes is restricted to within its genome, such modification may give rise to new – and unfamiliar – traits, as is clear from the examples above. Furthermore, the uncertainty associated with the impacts of a modified organism in an environment depends more on phenotypic changes and their interactions with that particular environment than on whether the organism has been created by intragenic or transgenic manipulation (Giddings, 2006).

Thus, intragenics are not ''familiar'' organisms. While they may share many features, and much DNA, with organisms with which we are familiar, where they have distinctive phenotypes, or are being introduced into new environments, they are essentially novel in character (Snow 2003).

4.3.1. *Risks to Health*

Perhaps the public's main concern about GMOs is whether they are safe to eat. The fact that GM food has been consumed for nearly two decades in some parts of the world, with scant evidence of negative health effects (Seralini et al., 2007), says little about its safety record given that there are no serious attempts to monitor the effects of consumption (Millstone et al., 1999; Burrows, 2001; Carman, 2004). Moreover, the long history of new products and technologies having unexpected health impacts that go undetected for decades suggest that it would be unwise to become too complacent about the level of risk involved in human consumption of modified foods (Burrows, 2001; Ferrara and Dorsey, 2001). The public's concerns about health effects are exacerbated when GM foods are not

labeled and intragenic products are unlikely to be labeled if they are not regulated (Schouten et al., 2006c, p. 1333).

The most obvious risks associated with the consumption of modified organisms revolve around the possibility of direct effects of any new genes or gene products, with the risk that these might increase the toxicity, allergenicity, and/or carcinogenicity of the modified food. The extent to which the products of intragenic modification generate these risks depends in part on whether there are any new proteins or other metabolic products associated with such modifications. Some intragenic organisms are likely to contain no new proteins, only different levels of proteins that are already present in the unmodified organism; even so, the presence of these proteins at altered levels might have implications for the extent to which it is safe to consume the modified organism. Moreover, some intragenics may contain proteins that are not normally consumed by humans, where new traits are transferred from related varieties that may not have been consumed by humans previously (De Cock Bunning et al., 2006). Finally, because there are numerous latent genes in any genome, a modification does not necessarily require new genetic material to result in production of new proteins or metabolites. Thus, for instance, ''up regulation'' of a normally latent gene may lead to the expression of a protein not normally expressed in that species. There is also the possibility that new genetic elements/modifications might have various indirect, pleiotropic effects on, for example, the secondary metabolism of a GM crop and that these may give rise to the production of novel metabolites and changes to nutritional composition (Schubert, 2002). Given that intragenic organisms may contain new proteins, or greatly altered levels of familiar proteins, they appear to generate similar concerns about health as transgenic organisms (Schubert and Williams, 2006).

4.3.2. *Risks to the Environment*

A second set of public concerns about products of gene technology relate to their environmental impacts. GMOs might have negative environmental impacts via a number of mechanisms: they might have environmentally significant non-target effects in their intended use; modified organisms might escape from their intended use and negatively affect surrounding ecosystems; new genetic elements could ''escape'' into other organisms as a result of gene transfer; finally, GMOs might have environmental impacts by virtue of shifts in agricultural practices associated with their use. While the risk of gene transfer may be lower with (some) intragenics, intragenic organisms seem capable of generating just as large impacts as transgenic organisms by any of the remaining three mechanisms.

A significant concern about the environmental impact of transgenics relates to their ''non-target'' effects. The introduction of a novel organism may generate a range of unpredictable effects in complex ecological settings that are difficult to anticipate or observe in small-scale trials. Questions about non-target effects have been raised in relation to the introduction of pesticidal traits such as Bt protein expression into plants in particular, as these may have impacts on non-target insects, such as butterflies, and on other non-target groups including soil microorganisms (Stotzky, 2000; Groot and Dicke, 2002). It is clear that the changed phenotype of an intragenic may result in non-target effects. Thus, for example, the role of ''ice plus'' bacteria in seeding rain and snow in clouds suggests that one unpredictable and unexplored risk of ice minus is a possible effect on climate (Piller, 1986). More recently, research has demonstrated the importance of ice plus bacteria in controlling agricultural insect pests (Castrillo et al., 2001) suggesting other potential impacts of ice minus.[10] When intragenic modifications significantly alter the phenotype, such as in growth-enhanced fish, this can lead to a range of effects on physiology and behavior that could lead to a variety of non-target effects. In intragenic, growth-enhanced, salmon effects included ''early hatch timing, shortened life cycles, precocious development of life history characteristics, and altered morphology, physiology, behavior, and viability'' (Devlin et al., 2004, p. 627). In exhibiting such effects, intragenic growth-enhanced fish are not distinguishable from transgenic growth-enhanced fish (Hallerman et al., 2007).

Another risk is that naturally occurring processes of horizontal gene transfer may lead to genes that were introduced by gene technology into one organism being transferred to other organisms. Horizontal gene transfer is routine in bacteria, which may mediate transfer to higher organisms such as plants and animals (van den Eede et al., 2004). Genes can also be transferred through vertical (sexual) gene transfer to close relatives of the GMO. Gene transfer may result in the disruption of ecosystems due to the ecosystemic effects of the altered phenotypes of organisms that have acquired the new genes; in agricultural contexts, weediness could have negative effects on agricultural management.

The risk of escape of new genes is partially alleviated by the development of intragenics, which, in most cases, do not involve the introduction of ''new'' genes. However, there are exceptions, when genes are moved from related varieties or strains, or when antisense genes or interference sequences are introduced. These added genetic elements have the potential for escape

[10] Despite these possibilities, there has been little ongoing monitoring or research on the actual effects of ice minus (we have been unable to locate any published papers on this topic in standard scientific journal databases).

and may have negative effects if transferred to other species. In particular, antisense genes could interact with homologous genes in related species, resulting in similar modifications. For example, the researchers involved in the ''daughterless carp'' project have acknowledged a low probability that the silencing mechanism they intend to employ may not be specific to carp and may be transferred via horizontal gene transfer to native fish species, thereby defeating the purpose of the project, which is ultimately to protect native species and ecosystems (Dall and Neumann, 2004).

The likelihood and impact of the escape of modified organisms themselves depends very much on the nature of the organism and their changed traits and seems unrelated to whether these traits are the result of intragenic or transgenic modification. There are numerous examples of non-genetically-modified organisms having significant negative impacts when introduced into new environments. Thus, for example, the carp that the ''daughterless carp'' project hopes to control are a destructive pest in Australian waters, despite being environmentally benign in their native Europe. It is clear that intragenic organisms have the potential to cause similar ecological disruption. For instance, growth-enhanced fish are larger throughout their life-cycle and may, therefore, feed on different size classes of prey; they may also be too large for the natural predators of their wild-type cousins. They may, therefore, threaten the survival of wild-type populations through competition, and of other species through competition and predation (Muir and Howard, 2004). Concerns about the ecological effects of genetically modified fish have lead researchers to devise means of containment of these fish via sterilization (Devlin et al. 2004; Nam et al. 2004). Once again, intragenic growth-enhanced fish are not exempted from ecological concerns by aquaculture researchers, who do not distinguish them from transgenic growth-enhanced fish (Hallerman et al., 2007).

Finally, the use of GMOs may have negative environmental impacts via effects on agricultural practices and environmental management. Critics have condemned the role played by GMOs in encouraging large-scale farming, monoculture, and the unsustainable use of natural resources (Levidow, 2005; Marsden, in press). The potential of GM technology to contribute to more sustainable forms of agriculture, particularly by reducing inputs (Russell, in press), is undercut by the dominance in the current commercial market of herbicide-tolerant crops and the overlap between the agricultural biotechnology and agrochemical industries (Crouch, 2001).

Unless intragenic modifications are associated with new paradigms of biotechnology research and application (Jefferson, 2001) and designed within a context of sustainable agriculture, they will not be exempt from this concern. Given that a relatively small number of large transnational companies, most of them at one time agrochemical companies, dominate

investment and activity in biotech research and development and that much of the public sector's involvement in developing GMOs has been in the context of collaborative links with these large companies, we suspect that the development of intragenic organisms will be shaped by the same concerns for profit over environmental sustainability that have proved so influential in the development of transgenics. Contemporary enthusiasm for the development of herbicide tolerance using intragenic modification gives us little reason at this stage to believe that the development of intragenics heralds a more sustainable trajectory for agricultural biotechnology. Instead, current indications suggest that intragenic modification may be taken up simply as a way to "invent around" regulatory and marketing problems. The extent to which this occurs may, however, be affected by the intellectual property status of intragenics (see Section 4.4).

4.4. *Intragenics and the Politics of Biotechnology*

There is another set of concerns about GMOs that are not captured by discussions of the health or environmental risks they may generate – and indeed are not adequately characterized as concerns about risk at all. They include political concerns about the control and ownership of biotechnology and their implications for agricultural and other communities, and also concerns about the ways in which science and technology shape human societies (and human beings) as they reshape the world.

An influential tradition of criticism of GMOs highlights the way in which the process of their development has encouraged – and in turn has been facilitated by – the development of intellectual property in living organisms – or perhaps more accurately, in the genetic code that determines their character (Shiva, 1997). The mere fact of the commodification of the genetic code offends some critics (Bodmer, 1992; Sagoff, 2002), whereas others object to the enrichment of the few at the expense of the many that the removal of property from the "genetic commons" makes possible (McNally and Wheale, 1996; Nelkin, 2002; Baumgartner, 2006) and the concentration of political and economic power that goes along with this.

Like other GMOs, intragenics seem all-too-conveniently to be novel enough to deserve patenting but not so novel that the public has any reason to be concerned about them (Pollan, 2003, p. 203). Under existing intellectual property regimes, patents on techniques relating to the creation of intragenics and their application are probably straightforward, and product patents or plant variety protection are likely to be sought for the intragenic GMOs themselves (but see below). Worries about commodification, therefore, seem not to be alleviated by the development of intragenics, which may in fact represent a faster and easier way to create a proprietary organism.

Similarly, in so far as research into intragenics is being undertaken by the same organizations that dominate the production and marketing of transgenics, a shift to intragenics is unlikely to address criticisms about the concentration of wealth and power in the hands of multinational corporations at the expense of local farmers and indigenous people.

However, the patenting of intragenics may not be entirely straightforward. The creation of some intragenics may involve no proprietary genes or gene constructs, if it involves "tweaking" or rearrangement of the existing genetic material of a species. The subtle changes associated with intragenic modification may make intragenics difficult to characterize as patentable inventions. This would presumably reduce private investment in the technology, but would open up advances in intragenic technology to public and non-profit organizations, particularly if intragenic modification became more technically routine. If development of intragenics turns out to be simpler and faster than the creation of transgenics, intragenic techniques – and the organisms arising from them – may be more accessible to publicly funded, small-scale, and resource-poor researchers and farmers than has been true of transgenics in the past. It is, therefore, possible that intragenics may play a role in democratizing biotechnologies and in tailoring technologies for environmentally and socially sustainable development (Jefferson, 2001; Buiatti, 2005). Such a role would, however, require changes in current priorities of public and global R&D (Cohen, 2001; Russell, 2001). Questions of health and environmental risk, discussed above, would also remain a considerable issue for any attempts to use intragenics in the pursuit of socially and environmentally sustainable development.

Finally, social and cultural impacts, particularly indirect impacts, of the introduction of GMOs represent a significant dimension of public concern about the development of transgenic – and possibly also intragenic – organisms (Bruce, 2002; Cormick, 2003). Scientific and technological advances not only transform the physical environment, they also have profound social and cultural impacts, both through social changes that the artifacts bring, and through changes to our understandings of the world and our place in it. Recent work on community level effects of GM crop use in Australia has revealed socially mediated impacts and risks related to the introduction of GMOs (Russell, in press). Just as new genes are expressed in a genetic and biochemical context that profoundly influences their function and the outcomes of their introduction, gene technologies are "expressed" in social, environmental, and political contexts that have a profound effect on the ultimate outcomes, contributions, and impacts these technologies have.

As well as the impacts on farming and agricultural practices discussed above, these impacts include changes in: employment, industry structure, demography, farmer control and dependency, community cohesiveness,

inequality, and social division. These impacts, which are broad social effects of technology and not unique to biotechnology, depend upon the particular GMOs, their traits, their fit with farming and agroindustrial systems, and interaction of these characteristics with social environments. There is no obvious distinction between transgenics and intragenics in relation to such impacts. For example, if new advances allow a range of production and consumption characteristics in intragenically modified plants (Rommens et al., 2004), commercialization of these will lead to a range of impacts on producers, rural communities, and consumers. These impacts could be mediated through, for example, changes in farm labor (herbicide replaces hand weeding in some crops), shifts in the use of agrochemicals and changes this brings to supply chains, changes to environmental management strategies (different traits are more or less compatible with integrated pest management {IPM}), and restructuring of industries and commodity markets (changes in shelf life affect competition between producers in different regions).

5. THE WAY FORWARD

We believe that there are significant risks associated with intragenics and deny that, as a group, they are necessarily any more natural and/or safer than transgenics. Despite being free of novel DNA, intragenics may have novel traits and therefore represent novel organisms in novel settings, potentially giving rise to novel hazards. Moreover, the use of recombinant DNA technology in intragenic modification renders the process of altering the organism much more akin to transgenic modification than to traditional breeding. In certain jurisdictions, notably Australia, organisms created by intragenic modification are not covered by regulations, and may not be brought to the attention of the public. There are calls for European regulations to also exempt intragenics from regulation (Schouten et al., 2006b). This is despite European regulations (and, to some extent, the Australian system) being considered more precautionary than other regulatory systems around the world. This regulatory gap is especially troubling given the likelihood that in the future researchers will be able to "invent around" regulations pertaining to transgenics by exploiting the considerable overlap between genomes of very different species and the new capacity provided by genomics to find desired genetic elements hidden within the genome of the species to be modified. We strongly recommend that intragenics be explicitly included in GMO regulations, and that GMO definitions be broadened to include them as is already the case in New Zealand.

The inclusion of intragenics within the process-based regulatory systems of Europe, Australia, and a number of other nations is relatively straightforward, and intragenic modification is still at an emergent stage, with few regulatory decisions having been made on intragenic applications. The proposed move to regulate intragenics may inhibit their development; but failure to do so could lead to a public backlash, and late and costly regulatory and mitigation measures, if intragenics do generate the potential impacts that regulatory systems are meant to protect us from.

Presumably, if this suggestion were to be taken up, intragenics would remain subject to those provisions in national regulatory regimes that allow exemptions, based on standards of safety and acceptability developed within their own countries, by which classes of GMO with a demonstrated history of use and safety can be exempted. At least items exempted from regulations generally remain to some extent contained and under ongoing scrutiny, compared with items excluded from regulations, which are simply not regulated. We suggest that new classes of GMO, such as intragenics, which "seem similar" to existing classes, should not be exempted until a record of safety is demonstrated. We believe that arguments to exclude intragenics from GMO regulations are based on spurious assumptions of safety and are driven by the pragmatic desire to limit regulatory burdens for science and innovation. While regulatory burdens and their effects on innovation are a relevant concern for technology governance, we believe that these concerns are overridden by the potential for intragenic modifications to give rise to traits that could generate novel hazards to the environment and to human health. Regulations are also essential to creating an environment of certainty and confidence for researchers, industry, and consumers.

We believe that the intragenics issue creates an opportunity for open and consultative debate and dialogue that would improve the confidence of citizens in regulations and science, and make up ground lost in the GM debate. Such dialogue could extend beyond discussions of risk to consider some of the political and social factors associated with the wider context of GMO development and use, such as industry consolidation, intellectual property protection, and technology transfer between rich and poor countries. These factors are critical to the risks and benefits arising from the technology, and influence public perceptions and the public acceptability of GM technology (Tokar, 2001; Bruce, 2002). They go well beyond the issue of whether GMOs are "natural," and extend to whether GMOs are useful and needed, and whether they contribute to sustainable development. These factors generally fall outside the remit of regulations and require a broad technology assessment approach for their analysis, that engages with moral arguments and with public opinion (Hoedemaekers, 2001). In the

meantime, regulations are crucial in assessing safety and protecting humans and the environment from the novel products of a powerful new technology.

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