Governance of Engineered Crop Plants: Any Lessons for Engineered Animal Governance?

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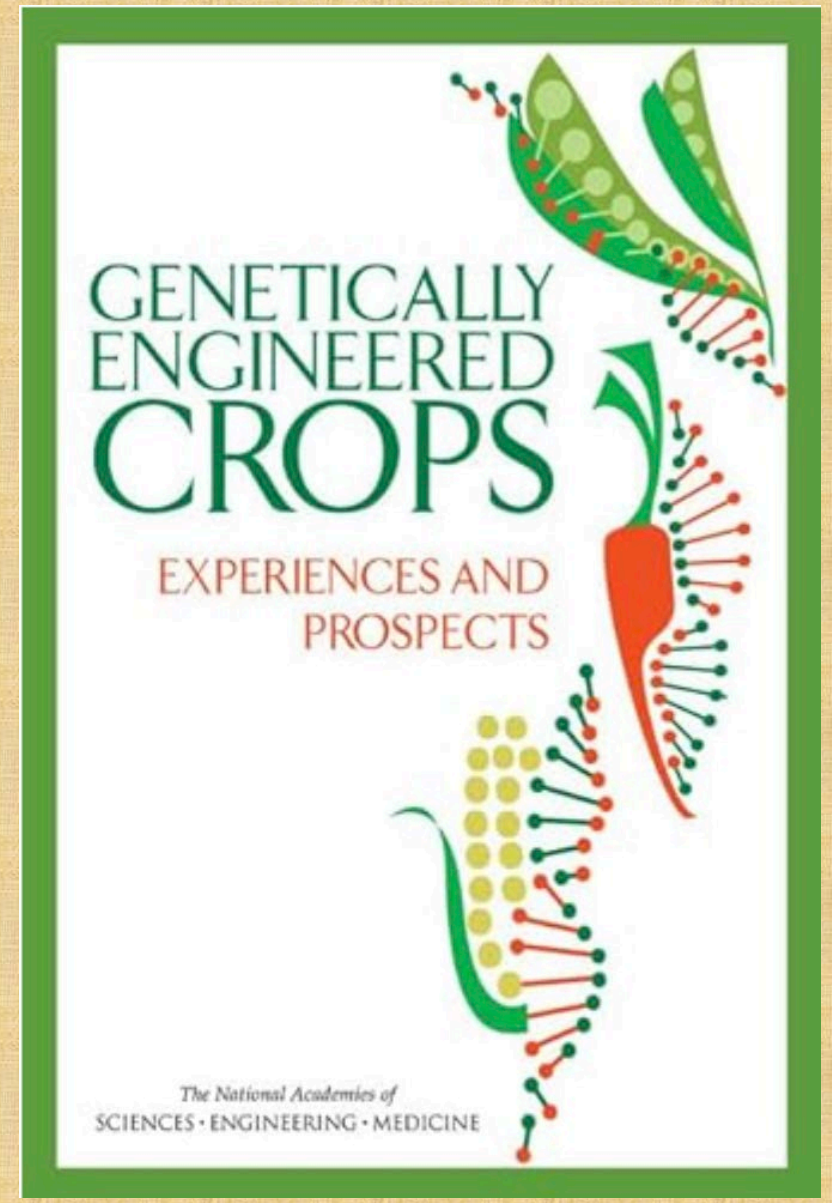
2016

20 Committee members -- 600 pages



2022

16 Authors. -- 3 pages

POLICY FORUM

AGRICULTURE

Toward product-based regulation of crops

Current process-based approaches to regulation are no longer fit for purpose

By **Fred Gould, Richard M. Amasino, Dominique Brossard, C. Robin Buell, Richard A. Dixon, Jose B. Falck-Zepeda, Michael A. Gallo, Ken E. Giller, Leland L. Glenna, Timothy Griffin, Daniel Magraw, Carol Mallory-Smith, Kevin V. Pixley, Elizabeth P. Ransom, David M. Stelly, C. Neal Stewart Jr.**

Much effort has been expended globally over the past four decades to craft and update country-specific and multinational safety regulations that can be applied to crops developed by genetic engineering processes, while exempting conventionally bred crops. This differentiation made some sense in the 1980s, but in light of technological advances, it is no longer scientifically defensible. In the coming decades, innovations in genetic engineering and modern "conventional" processes of crop development will enable use of these approaches to alter more crops and more traits. Future governance of new plant varieties and foods, regardless of the processes and techniques used to develop them, will require new, scientifically sound assessment methodologies, developed in a manner acceptable to society. Here, we provide a rationale for one governance approach that moves away from current process-based regulation and uses newly developed molecular techniques that enable detailed characterization of the new crops and foods themselves.

CLINGING TO PROCESS

A 2016 report from the US National Academies of Sciences, Engineering, and Medicine (NASEM) on genetically engineered (GE) crops (which we coauthored) stated, "Emerging genetic technologies have blurred the distinction between genetic engineering and conventional plant breeding" [(*1*), p. 3]. In the past few years, this blurring has increased and resulted in a number of governments struggling to redefine what constitutes a GE plant in need of regulation. Newly enacted and proposed regulations aimed at addressing this problem vary dramatically (*2*), especially with regard to CRISPR-based genetic changes.

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The European Union (EU) considers any crop with a CRISPR-based modification as GE and subject to regulation, whereas other governments, to varying degrees, trigger regulation on the basis of the size of the genetic change and the source of the inserted genetic material (*2*). A recent EU government study of its regulations for gene editing concluded, "There are strong indications that [EU legislation] is not fit for purpose" and that additional work is needed "in order for the legislation to be resilient, future-proof and uniformly applied as well as contribute to a sustainable agri-food system" [(*3*), p. 59]. We argue here that the same conclusion is warranted for all current and recently proposed risk assessment systems that use size and source of inserted genetic material to determine the requirement for safety testing.

The recent revision to US government safety regulation of new crop varieties and foods provides an example. Although the United States acknowledges the need to focus on the biological characteristics of new plant products, the reality is that the specific technological approach used to develop the product has generally determined whether a new variety is subject to federal regulation. The 2020 US Department of Agriculture (USDA) rule on plant biotechnology (*4*) and the proposed rule by the US Environmental Protection Agency (EPA) for pesticidal plants (*5*) solidify the role of process by exempting from regulation conventionally bred varieties as well as GE plant varieties with new genetic material that could theoretically have been transferred to the variety through conventional breeding (defined broadly to include mutation breeding, embryo rescue, protoplast fusion, and newer techniques).

The assumption is that we have long familiarity with conventional breeding processes and can therefore assume that they are safe. It is noteworthy that the new US rule for labeling GE products (*6*) does not even define conventional breeding, in part because "attempting to do so may cause confusion in light of the rapid pace of innovation." That comment makes obvious the logical difficulty with basing regulations on that criterion: There cannot be long familiarity with something that is rapidly changing. Indeed, major plant breeding corporations are shifting to a new "conventional" approach called genomic selection (*7*), in which vast, combined, genomic, phenotypic, and environmental databases are used as guides for breeding new varieties with new combinations of genetic materials. Such combinations could not have been produced with conventional breeding approaches that were available when initial regulations to differentiate conventional versus GE crops were developed.

As with conventional breeding, methods for genetic engineering of crops have also changed. The first widely commercialized GE crops in 1996 all involved the transfer of DNA from one or more donor species into a recipient crop ("transgenic"), with the initial placement in the genome being random for the most part. Given the novelty of these crops, there was concern that the engineering would result in unintended changes to the genome that could not be discerned with existing genetic methods but could cause risk to the environment or health. Critics contended that the testing conducted was inadequate to demonstrate that GE foods were safe. At the time, health safety testing for targeted and off-target changes typically involved measurement of approximately 70 plant-produced chemicals and chemical groupings, as well as limited testing on rodents (*1*). Among the concerns raised were that plants produce thousands of bioactive compounds that were not being monitored, and that unintended changes in these compounds could cause allergies or other illnesses.

Today, genetic engineering technologies based on CRISPR and other site-directed nucleases (SDNs) can substantially alter the properties of a plant by making changes in a single nucleotide in a specific genomic location and by inserting or deleting genetic sequences of varied sizes (*2*). Arguments have been made that such "gene editing" is in most cases safe and does not require the kind of safety testing that is done with plants developed by using earlier genetic engineering technologies (*1*). Argentina was one of the first countries to implement legislation that exempts most SDN changes from safety testing (*2*).

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In the past we used **Process** to predict potential for risk.

Today we can directly measure the **Product**.

POLICY FORUM

AGRICULTURE

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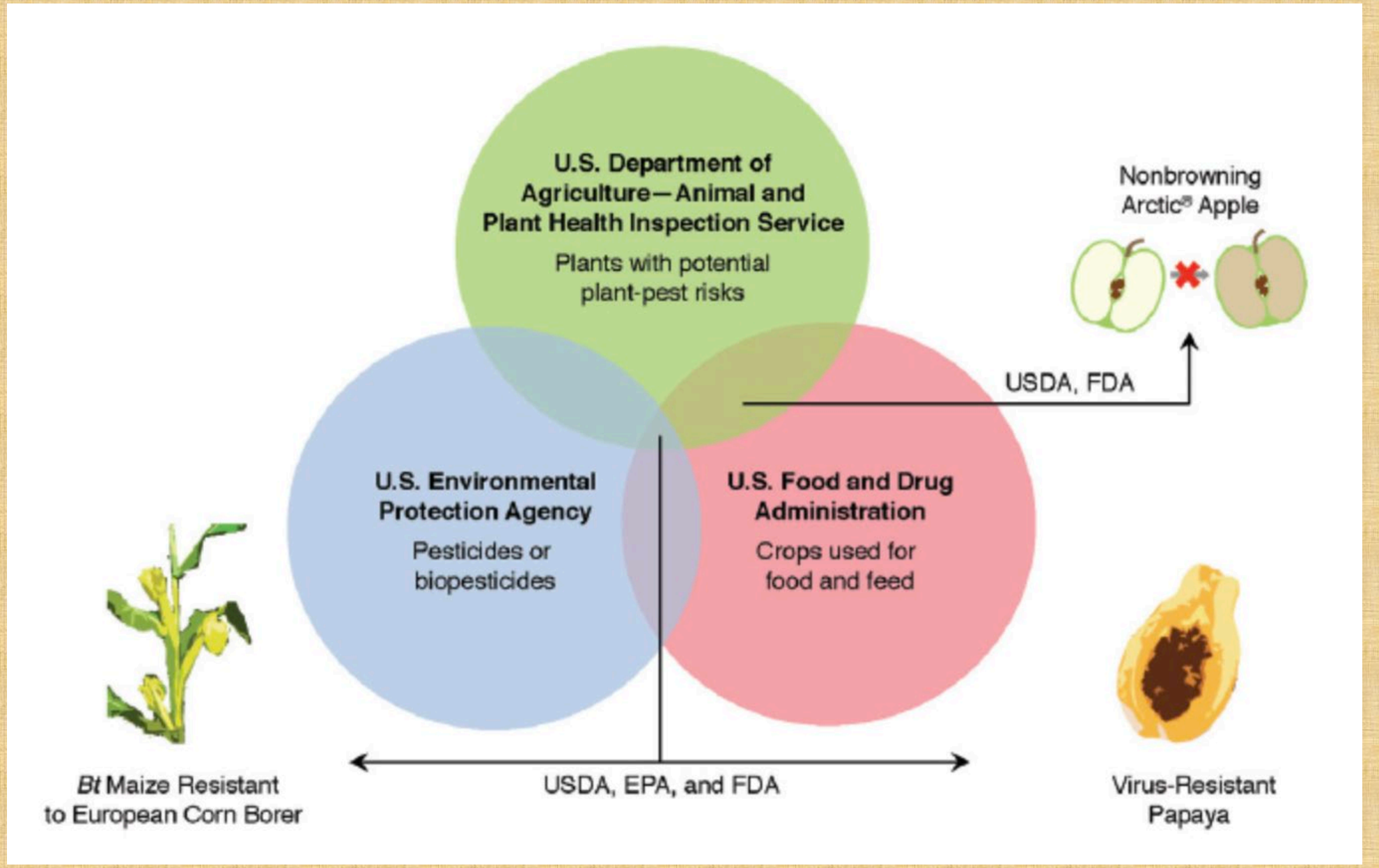
Science

1984 ----------2024

40 years

Average age in US = 38.9 years

Coordinated Framework for Biotechnology



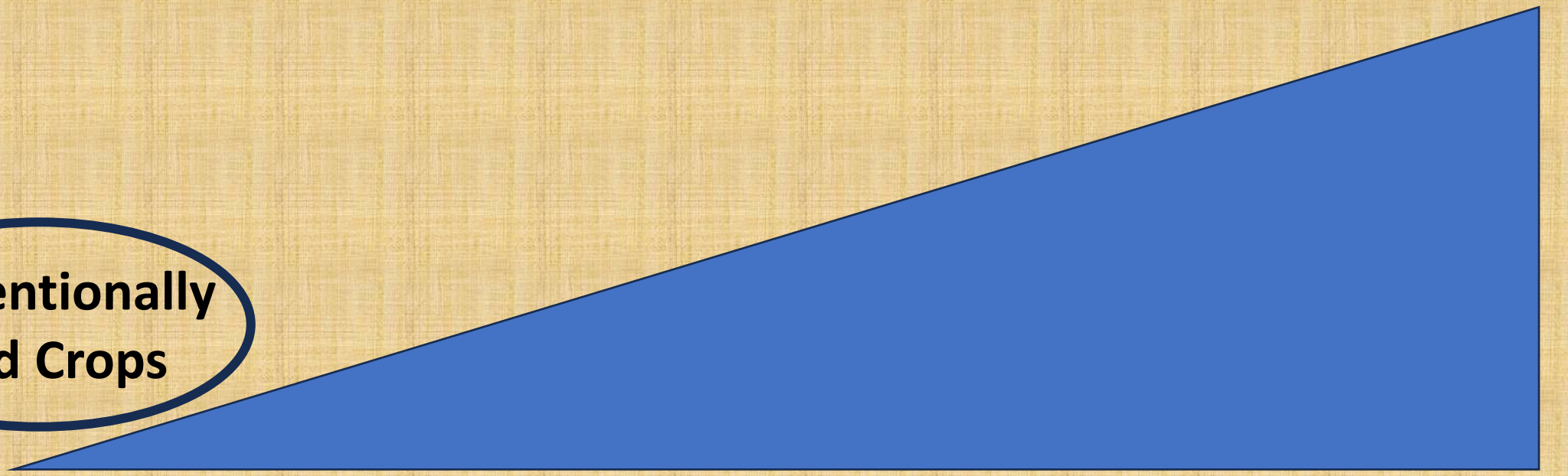
Substantial Equivalence

Safety of a new food may be assessed by comparing it with a similar traditional food that has proven safe in normal use over time.

Extent of Global Regulatory Oversight

1995-1996

Transgenic Crops



Conventionally Bred Crops

Extent of Global Regulatory Oversight

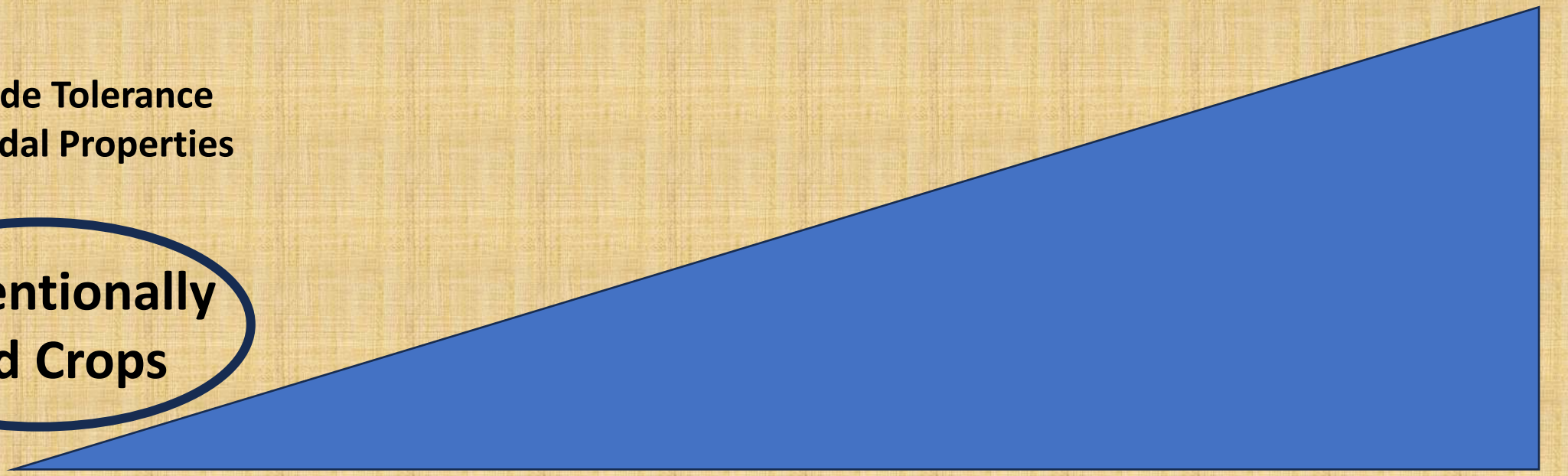
1995-1996

Herbicide Tolerance
Insecticidal Properties

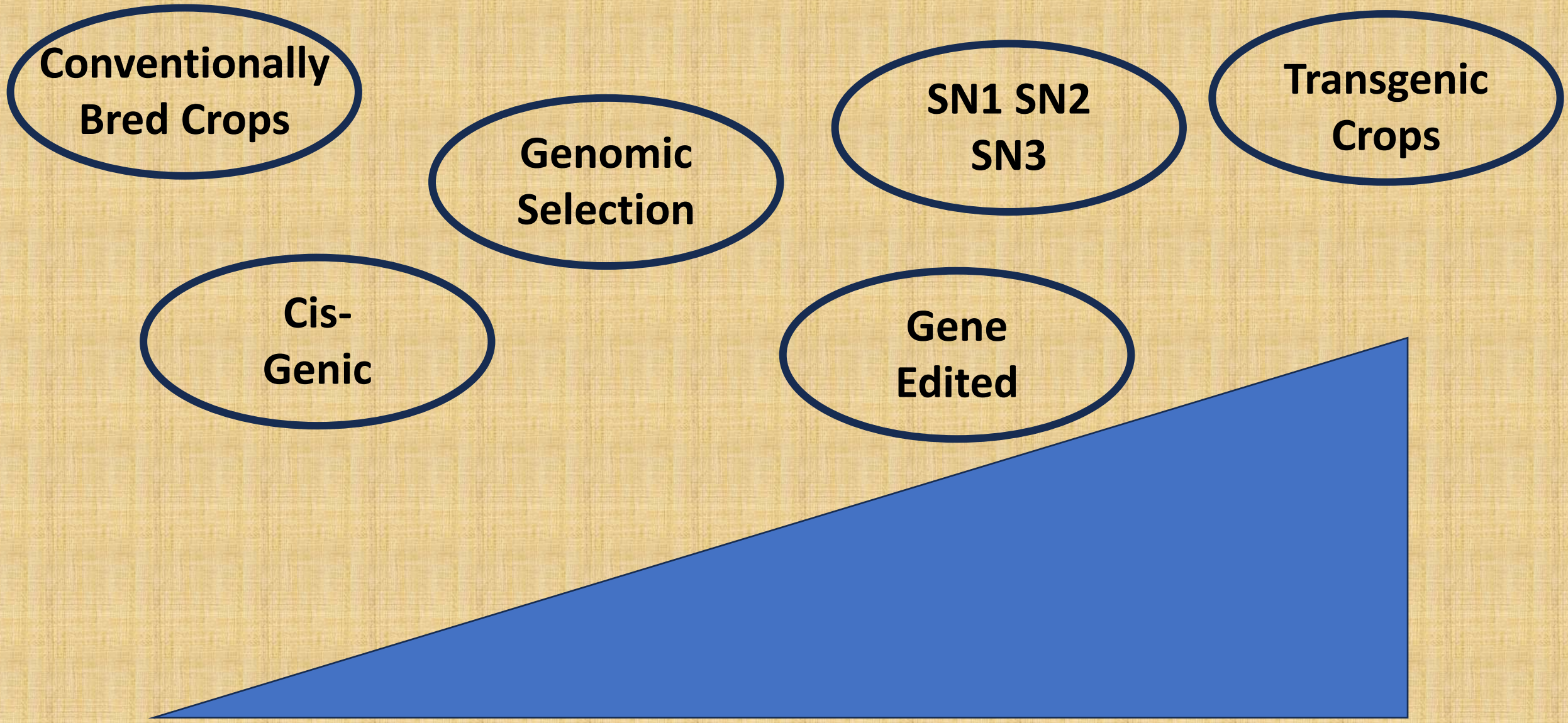
Transgenic Crops

Herbicide Tolerance
Insecticidal Properties

Conventionally Bred Crops



“Emerging genetic technologies have blurred the distinction between genetic engineering and conventional plant breeding”



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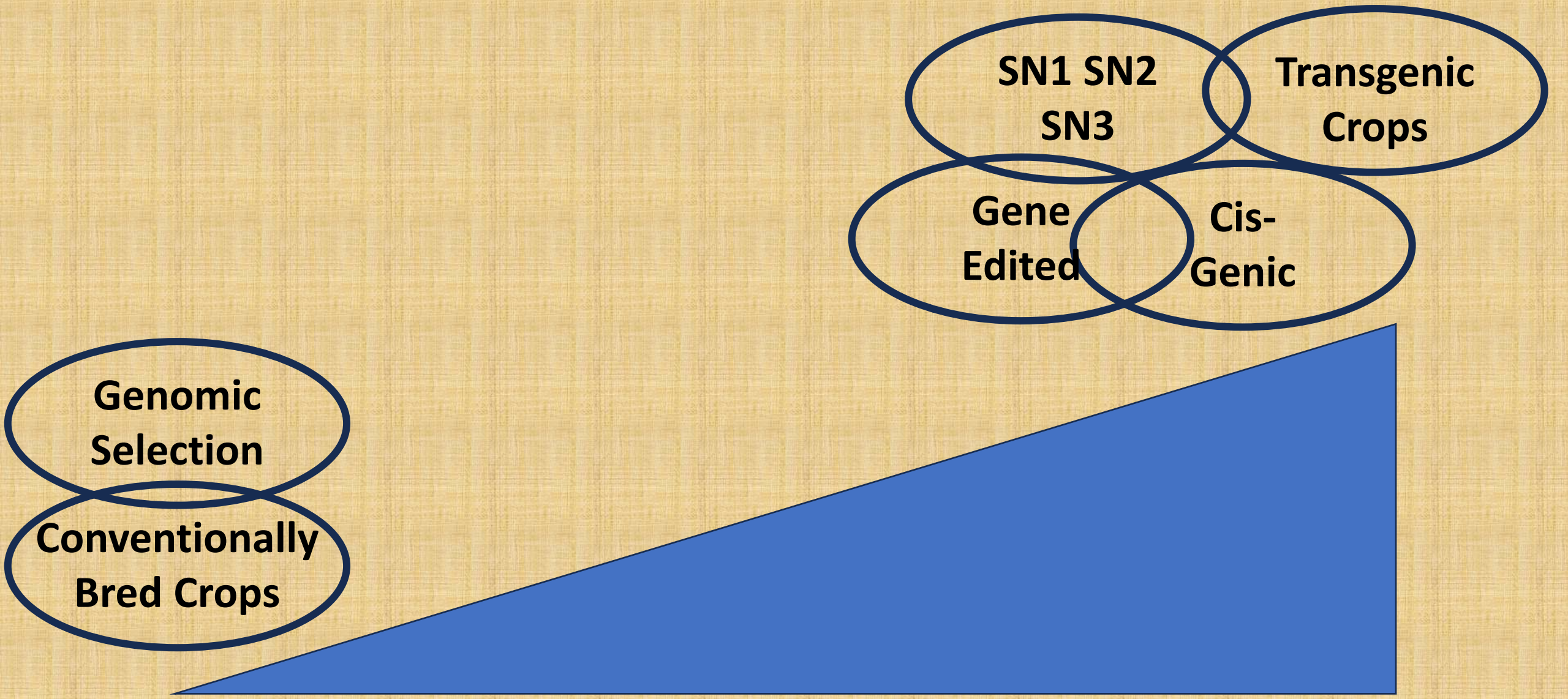

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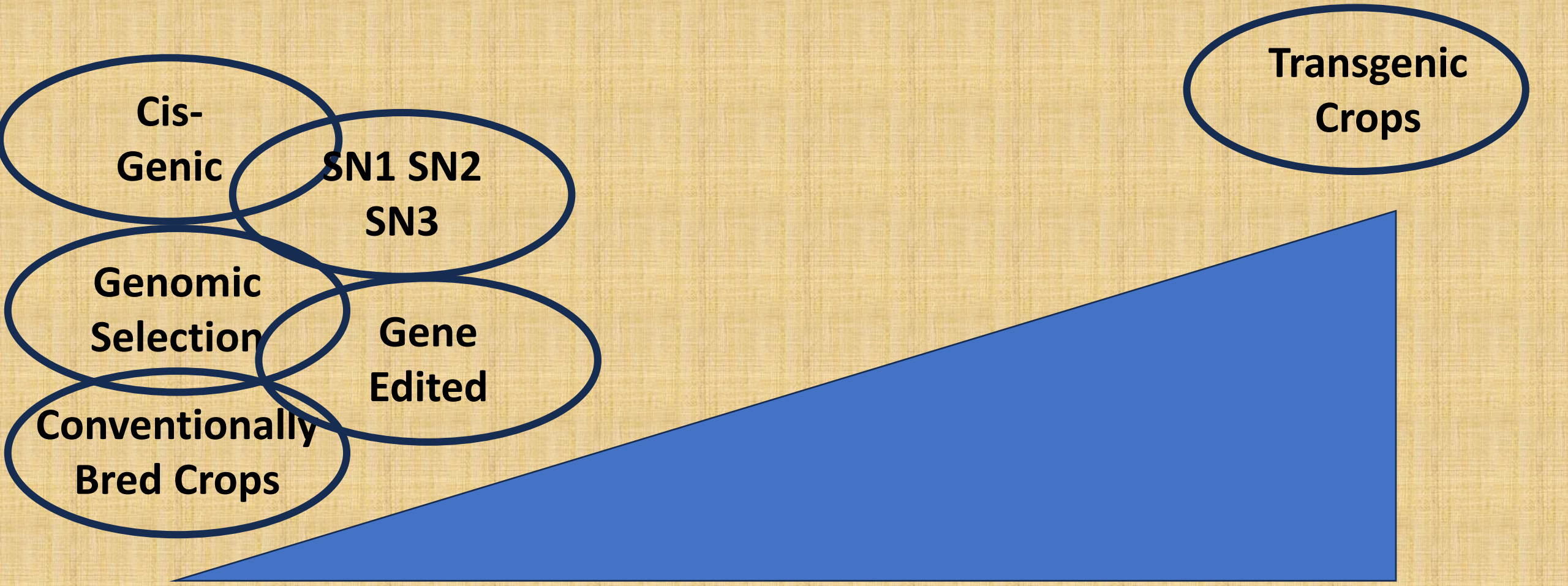


USDA-APHIS-2020
Exemptions

1) **Genes from wild relatives**

(or corresponding to them)

2) **Single base pair substitutions**

3) **DNA breaks**

(with non-homologous end joining)

Because such changes could occur by conventional breeding (including mutagenesis breeding) and should therefore be safe

Cisgenic

Wild Tomato Species

Cultivated Tomato

Solanum Lycopersicoides

"The ultra-resistant wild tomato"

Lycopersicon esculentum

Cisgenic Transgenic

Wild Tomato ***Cultivated Tomato*** ***Cultivated Bell Pepper***

Solanum Lycopersicoides ***Lycopersicon esculentum*** ***Capsicum annuum***

"The ultra-resistant wild tomato"

The US rule for labeling GE products doesn't define conventional breeding, in part because…

"…attempting to do so may cause confusion in light of the rapid pace of innovation."

The US rule for labeling GE products doesn't define conventional breeding, in part because…

"…attempting to do so may cause confusion in light of the rapid pace of innovation."

This is not your Father's conventional breeding, and it won't be your daughter's conventional breeding

USDA-APHIS-2020
Exemptions

1) Genes from wild relatives

(or corresponding to them)

2) Single base pair substitutions

3) DNA breaks

(with non-homologous end joining)

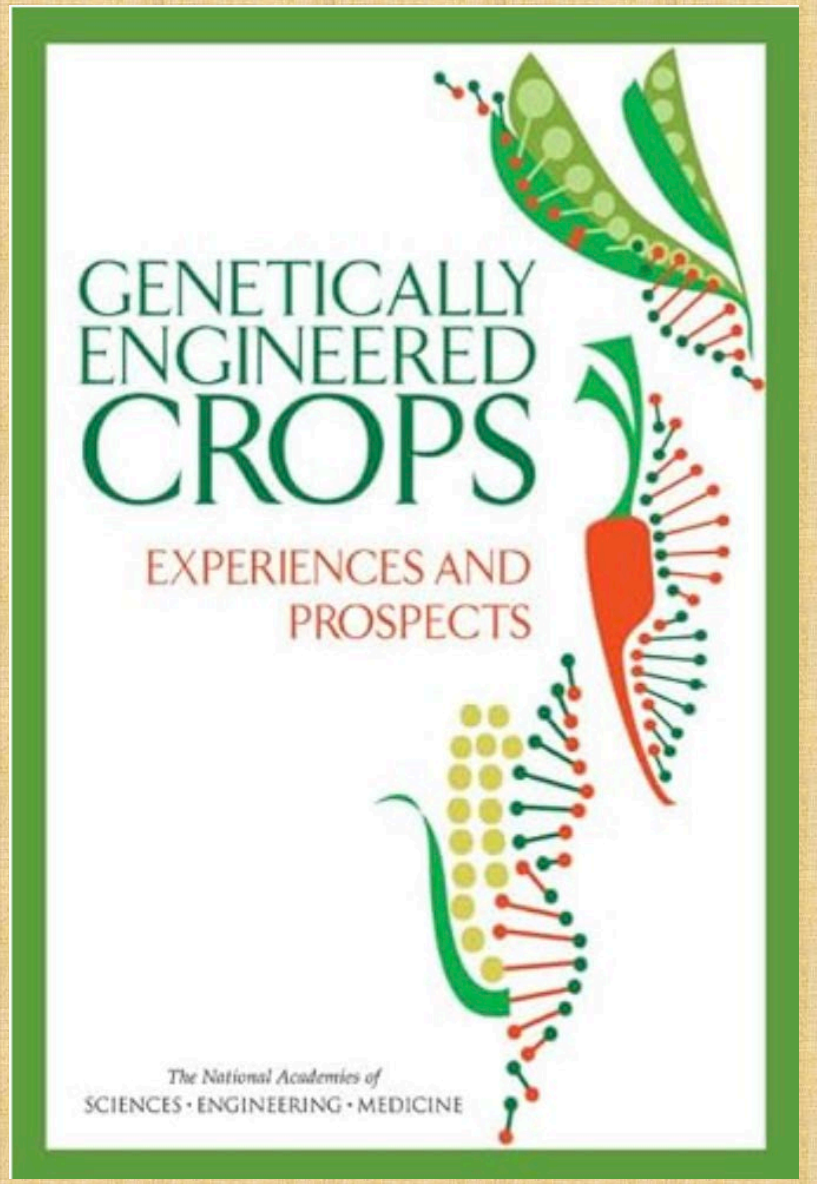
Because such changes could occur by conventional breeding (including mutagenesis breeding) and should therefore be safe

USDA-APHIS-November 2023
Updated Exemptions

Plants with up to four modifications made simultaneously or sequentially, with each being at a different genetic locus.

2016

“The size and extent
of the genetic transformation
itself has relatively little
relevance to its biological
effect and consequently,
its environmental or food
safety risk”



EPA-- May 31, 2023

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 174

[EPA–HQ–OPP–2019–0508; FRL–7261–04–OCSPP]

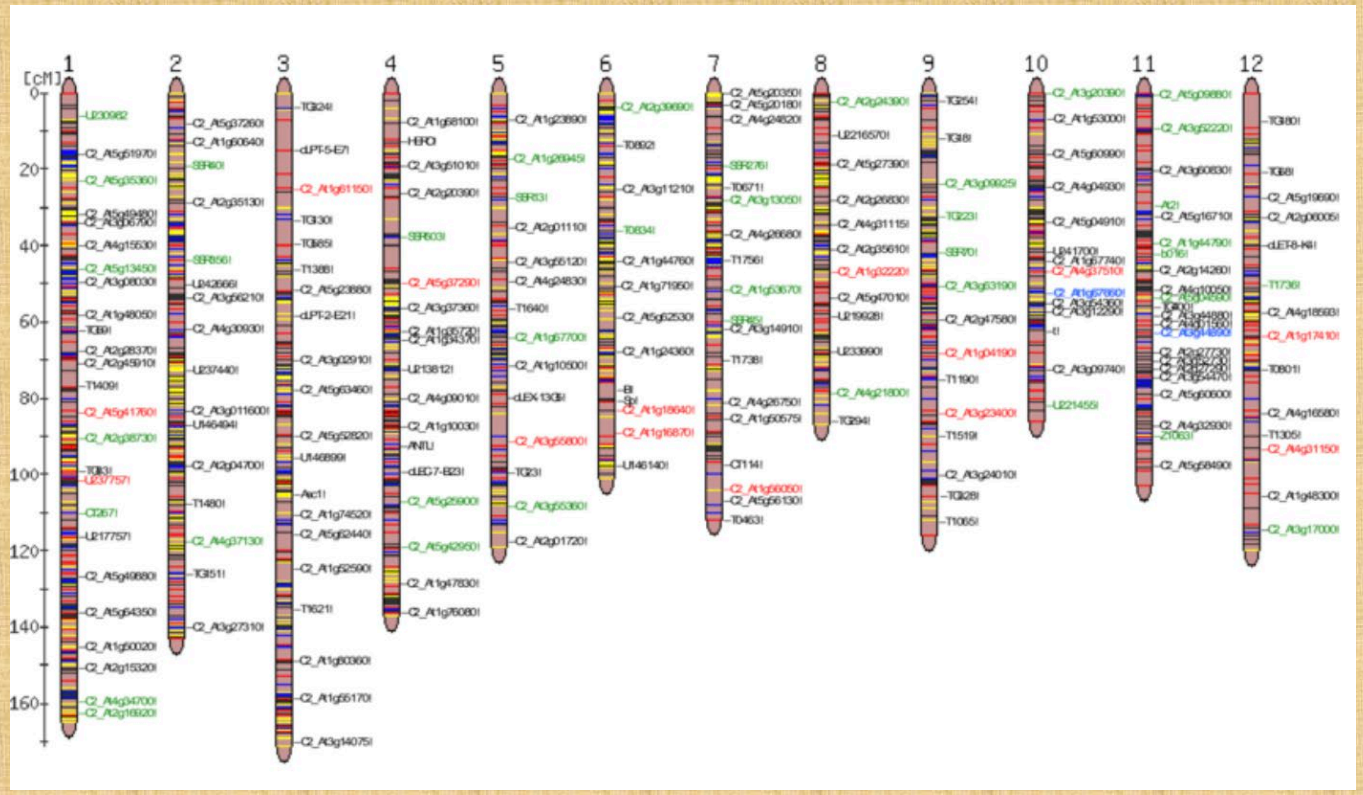
RIN 2070–AK54

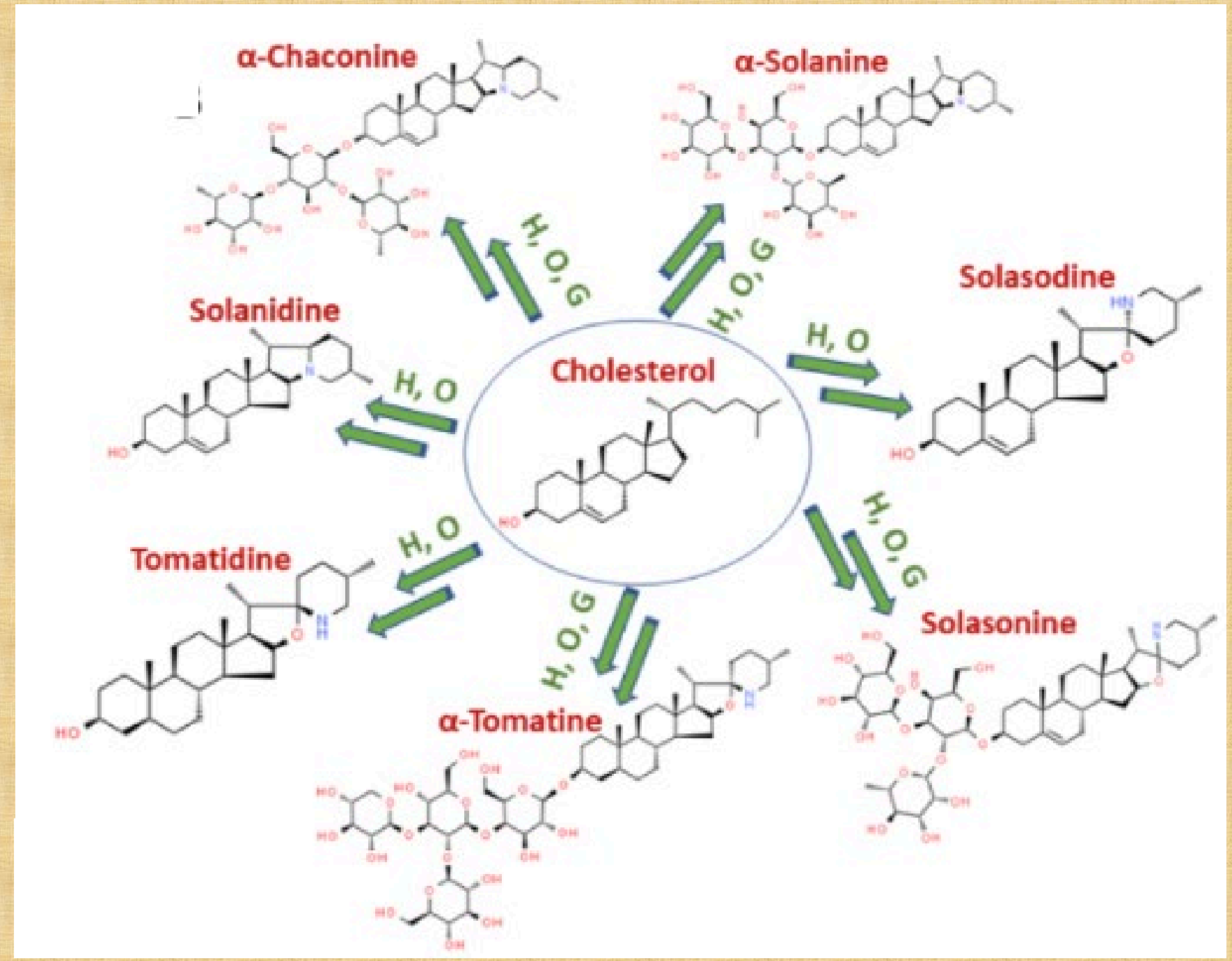
Pesticides; Exemptions of Certain Plant-Incorporated Protectants (PIPs) Derived From Newer Technologies

AGENCY: Environmental Protection Agency (EPA).

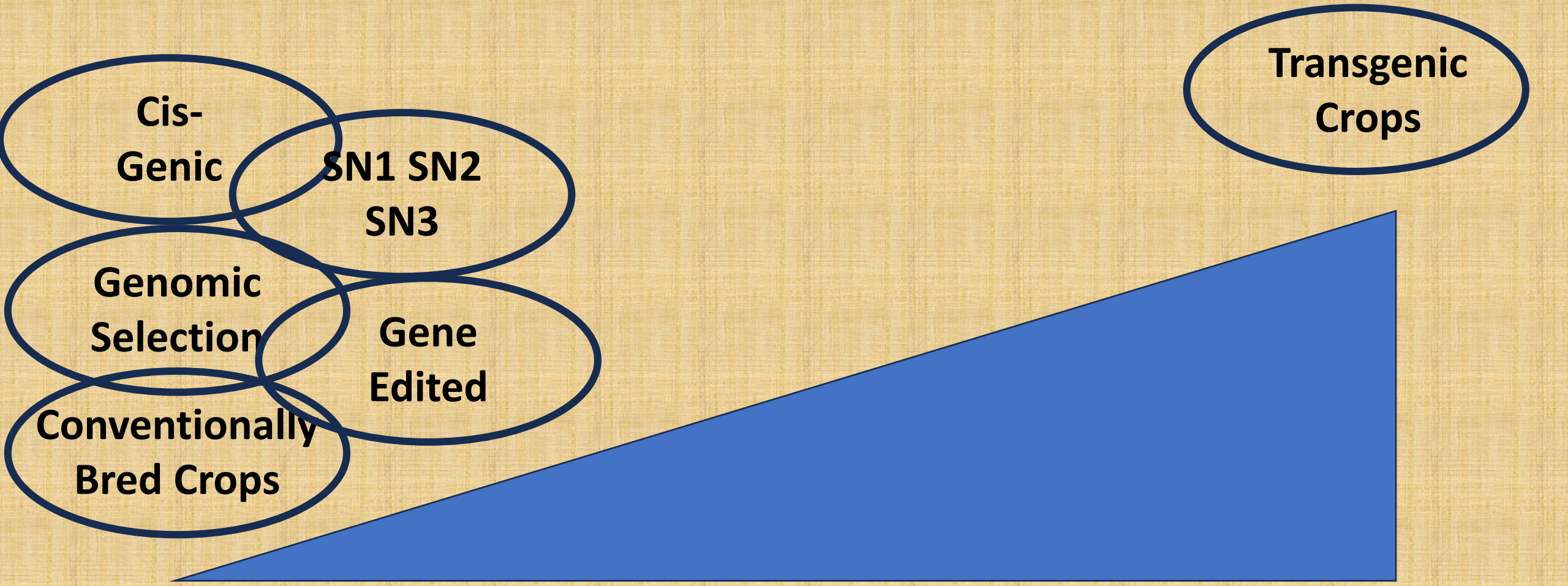
ACTION: Final rule.

Tomato Chromosomes

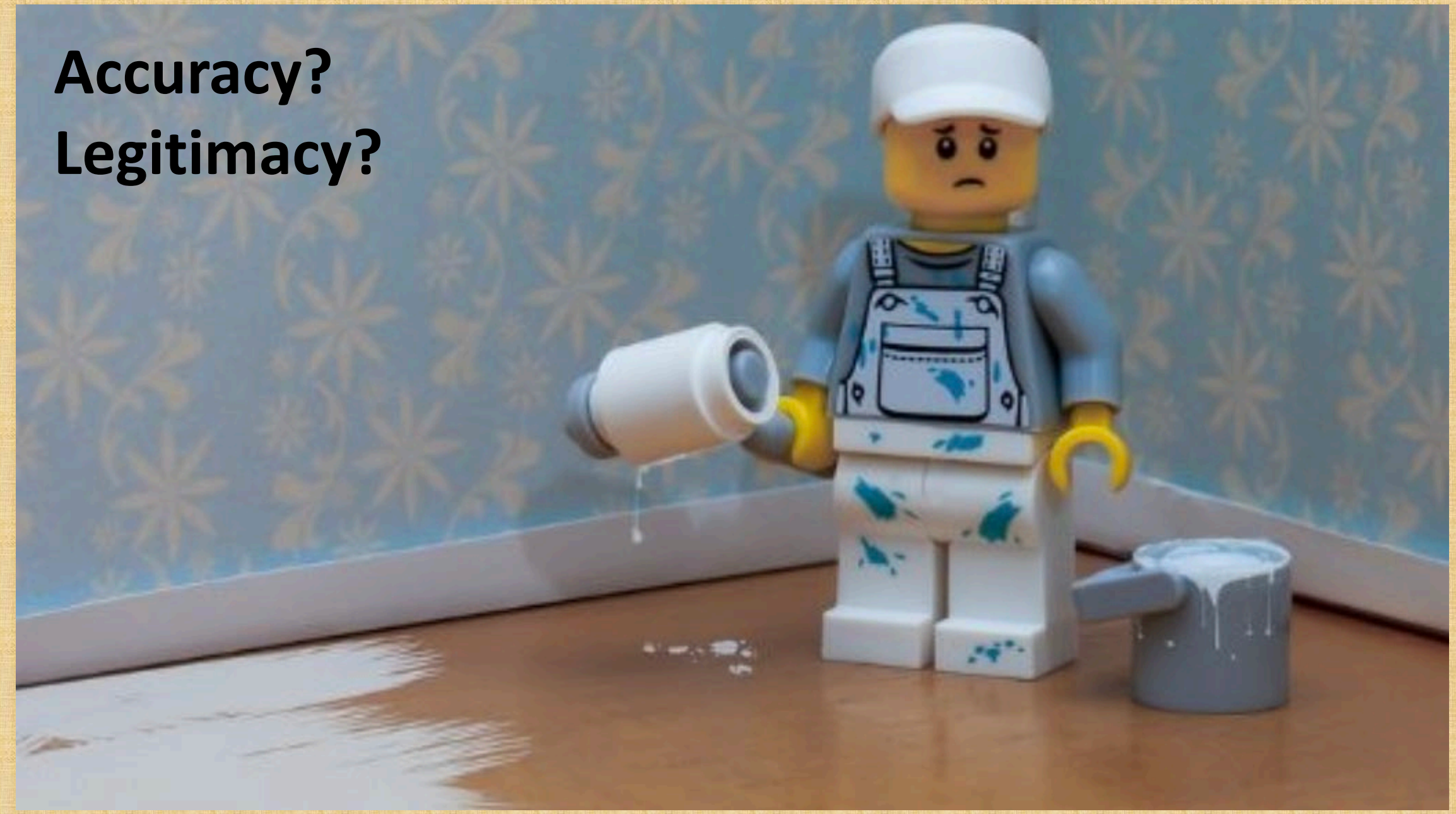



α-Chaconine
α-Solanine
Solanidine
Cholesterol
Solasodine
Tomatidine
α-Tomatine
Solasonine
H, O, G
H, O

Extent of Global Regulatory Oversight



Accuracy?
Legitimacy?



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2022

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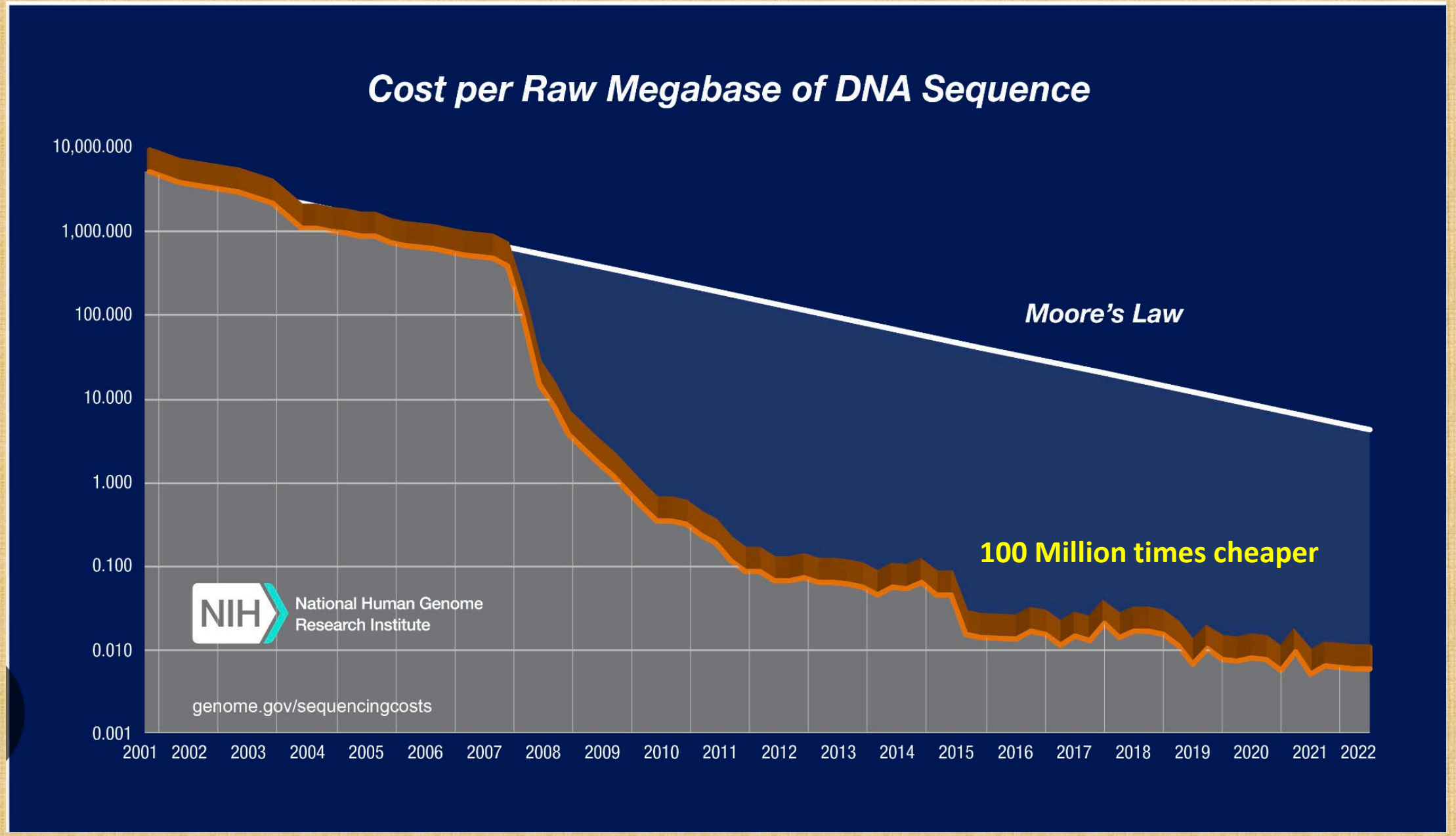
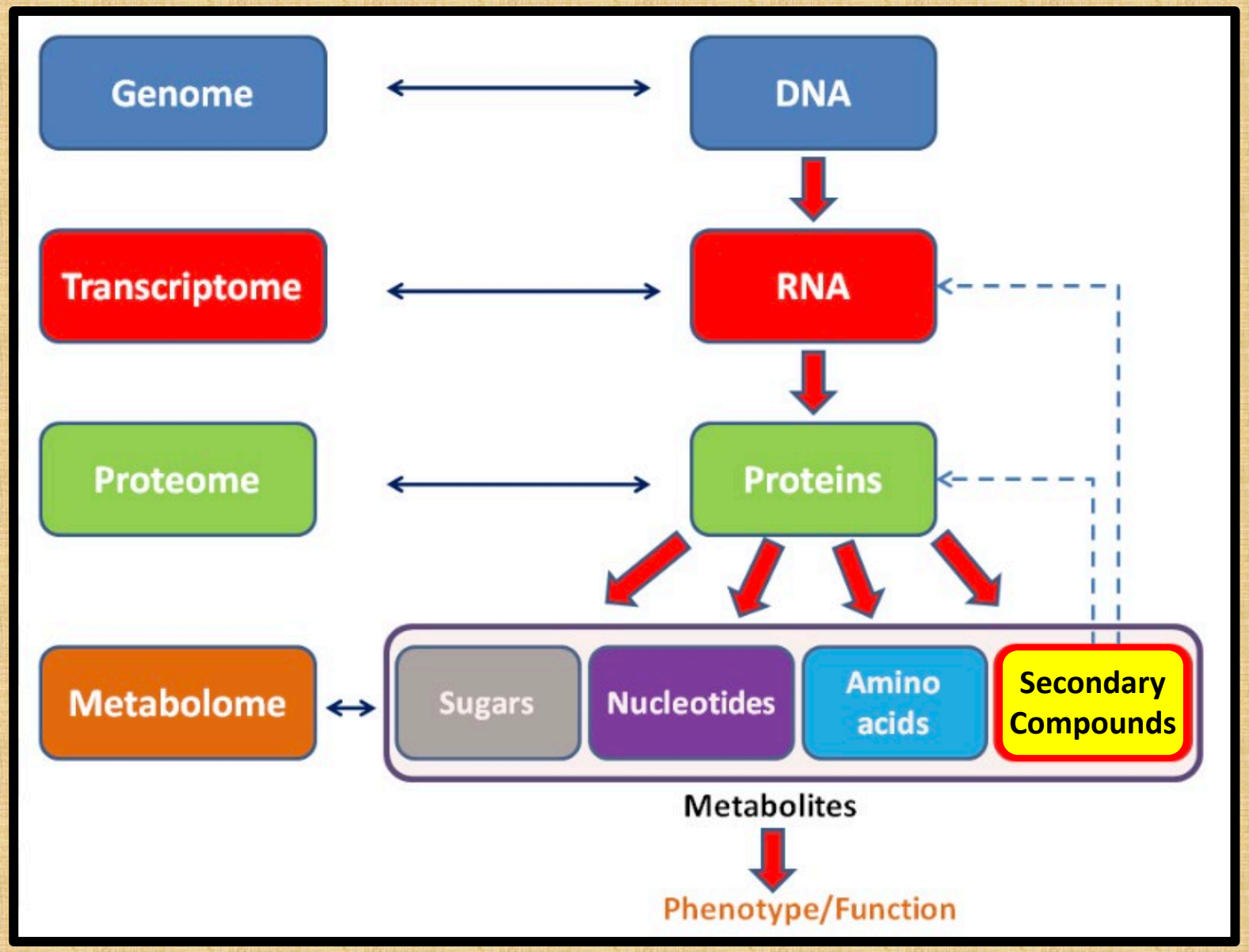
1984 ----------2024



Moore's Law = number of transistors in a computer chip doubles every two years

-omics can “fingerprint” the product



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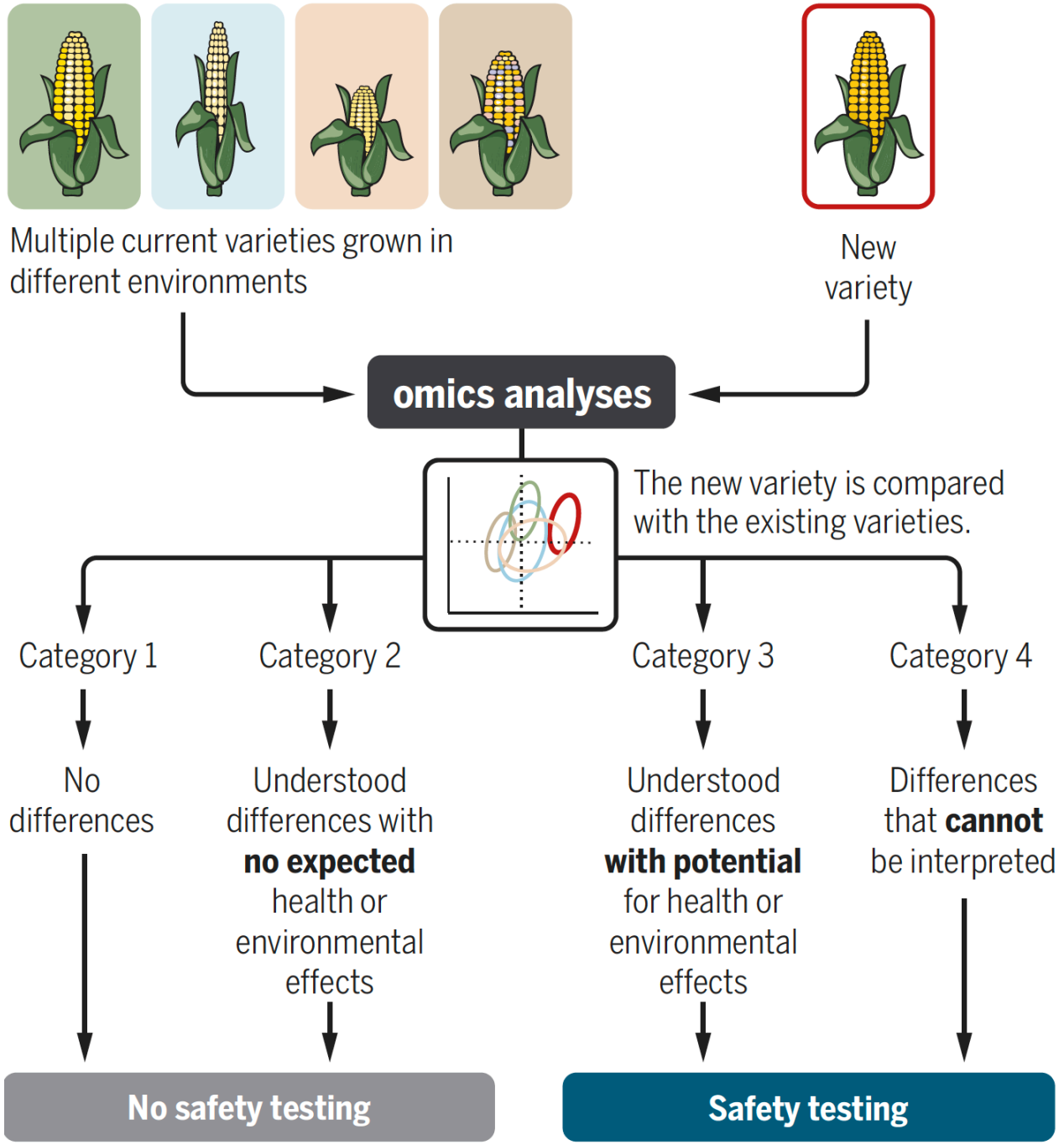
Multiple current varieties grown in different environments
New variety
omics analyses
The new variety is compared with the existing varieties.
Category 1
Category 2
Category 3
Category 4
No differences
Understood differences with **no expected** health or environmental effects
Understood differences **with potential** for health or environmental effects
Differences that **cannot** be interpreted
No safety testing
Safety testing

Caveat

“Recognizing that these new measurement technologies could be used in ways that would over- or underregulate new crops and foods….

…..we see the need for a multistep process to develop a new, overall approach for governance of new crop varieties and foods.”

Caution

Avoid Taco Shell Syndrome

Caution

Avoid Taco Shell Syndrome

Loss of Legitimacy

Is there a place for -omics approaches for establishing Substantial Equivalence in engineered food animals?





It might be a lot simpler than with crops

nature International weekly journal of science

ILLUSTRATION BY DAVID PARKINS

Science can't solve it

Democratically weighing up the benefits and risks of gene editing and artificial intelligence is a political endeavour, not an academic one, says **Daniel Sarewitz**.

This year, several leading researchers have sounded warnings about the

and others wrote last year of CRISPR that "the decision of when and where to apply

is necessary to learn how to accentuate the positive aspects of AI and avoid its potential

Other Potentially Relevant Recommendations Related to Testing

1) It is important to justify the size of a difference between treatments that will be considered biologically relevant.

2) A power analysis based on within treatment standard deviations …. should be done … to increase the probability of detecting differences that would be considered biologically relevant.

§ 174.95 Documentation for an exemption for a plant-incorporated protectant created through genetic engineering from a sexually compatible plant.

If the source plant is a wild relative of the recipient plant, describe why the plant-incorporated protectant is not anticipated to pose a hazard to humans or the environment (*e.g.,* Are levels of the pesticidal substance produced in the recipient plant within the ranges of levels generally seen in plant varieties currently on the market and/or known to produce food safe for consumption? Is the pesticidal mode of action non-toxic? Does the plant-incorporated protectant lack sequence similarity to known mammalian toxins, toxicants, or allergens? Is the plant-incorporated protectant a commonly screened substance and therefore familiar to plant breeders?).

it is not required that all regulatory regions be inserted,
but those that are inserted must meet the criterion (of being identical)

Food for human consumption and animal drugs, feeds, and related products: Foods derived from new plant varieties; policy statement, 22984

Vol. 57 No. 104 Friday, May 29, 1992 p 22984 DEPARTMENT OF HEALTH AND HUMAN SERVICES

"…..the key factors in reviewing safety concerns should be the characteristics of the food product, rather than the fact that the new methods are used.

"Substances that are expected to become components of food as result of genetic modification of a plant and whose composition is such or has been altered such that the substance is not generally recognized as safe (GRAS) or otherwise exempt are subject to regulation as "food additives"…"