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Expertise in support to public policies: a few insights from the GMO / NBT case

Yves Bertheau

Inra – MNHN

April, 9 2018

ISYEB MNHN Seminar



MUSÉUM
NATIONAL D'HISTOIRE NATURELLE



History and general context

- Several European crises (contaminated blood, mad cow, from Chernobyl's assertions to NDDL or long term nuclear wastes storage),
- Several French crises with merging of medicine / pharmaceuticals committees,
- Outcomes: establishment of US then European and French risk assessment commissions then agencies, toward a “professionalization” of the expertise,
- Several stakeholders and experts' resignations such as in 2016 the Inserm's CEO from the nutritional labeling Committee.
- A number of catchy titles ('High council', 'high authority', 'high level'...) inflating as controversies swell,
- The European SAM creation, 'France stratégie' call for contribution on the crisis of the expertise, FRB testing a rather unusual expert elicitation method...

Tableau 3 — Dans quelle mesure êtes-vous d'accord pour que l'application suivante soit encouragée : utiliser la biotechnologie moderne dans la production de nourriture, par exemple pour augmenter son taux de protéine, prolonger sa conservation ou améliorer son goût ? (% de réponses « Tout à fait d'accord » et « Plutôt d'accord » en 1996, 2002, 2005 et 2010, parmi les États membres de l'UE)

1996		2002		2005		2010	
Finlande	59	Finlande	47	Rép. tchèque	46	Grande-Bretagne	35
Pays-Bas	56	Espagne	42	Portugal	38	Rép. tchèque	35
Portugal	55	Portugal	39	Malte	36	Slovaquie	32
Espagne	53	Grande-Bretagne	37	Finlande	35	Danemark	29
Italie	47	Suède	34	Espagne	34	Pays-Bas	27
Belgique	47	Allemagne	32	Italie	34	Finlande	27
Grande-Bretagne	45	Irlande	32	Slovaquie	30	Hongrie	27
Irlande	45	Danemark	31	Grande-Bretagne	30	Espagne	27
Grèce	43	Belgique	31	Irlande	29	Suède	26
Allemagne	41	Pays-Bas	30	Danemark	28	Belgique	26
France	39	Autriche	28	Belgique	27	Pologne	25
Suède	34	Italie	26	Pays-Bas	25	Portugal	25
Luxembourg	31	Luxembourg	22	Lituanie	23	Estonie	23
Danemark	30	France	19	Hongrie	23	Autriche	21
Autriche	18	Grèce	18	Pologne	23	Irlande	21
Ensemble	44	Ensemble	32	Suède	22	Allemagne	20
				Allemagne	21	Italie	20
				Autriche	21	Slovénie	20
				France	20	Malte	17
				Slovénie	20	Luxembourg	15
				Estonie	19	France	14
				Chypre	17	Lettonie	12
				Lituanie	15	Roumanie	11
				Grèce	14	Bulgarie	11
				Luxembourg	8	Lituanie	10
				Ensemble	27	Grèce	9
						Chypre	5
						Ensemble	23

Lecture : en gras bordeaux figurent les pays au sein desquels existent des cultures de plantes transgéniques.

Tableau 6 — Attitudes à l'égard de la nourriture GM et des nanotechnologies selon la socialisation à la science en 2010 (%)

	Socialisation à la science			Total
	Non famille non ego	Famille ou ego	Famille et ego	
Encourager la nourriture GM				
Sans réponse	20	15	10	16
Accord	20	23	29	23
Désaccord	60	62	61	61
Total	100	100	100	100
Encourager les nanotechnologies				
Sans réponse	42	32	23	35
Accord	32	43	53	40
Désaccord	26	25	24	25
Total	100	100	100	100

Tableau 7 — Attitudes à l'égard de la nourriture GM et des nanotechnologies selon le degré d'information en 2010 (%)

	Degré d'information			Total
	Pas entendu parler	Entendu parler, pas discuté	Entendu parler, discuté	
Encourager la nourriture GM				
Sans réponse	38	17	7	16
Accord	17	22	26	23
Désaccord	45	61	67	61
Total	100	100	100	100
Encourager les nanotechnologies				
Sans réponse	50	23	8	35
Accord	23	52	74	40
Désaccord	27	25	18	25
Total	100	100	100	100

Les Français confiants dans la science, moins dans les chercheurs

La science est perçue par les Français comme bénéfique pour la société et pour eux-mêmes. Mais la confiance qu'ils témoignent à cette activité est d'autant moins marquée qu'il s'agit de personnes comme plus liées à des intérêts industriels et financiers.

Tel est l'enseignement le plus marquant d'un sondage réalisé par Ipsos/CGI pour Le Monde, le magazine La Recherche et le ministère de l'Enseignement supérieur et de la recherche auprès de 1 004 personnes interrogées par Internet entre le 10 et le 16 avril. Cette enquête sera présentée au Collège de France, jeudi 23 mai, lors du Forum Science, recherche et société organisé par La Recherche et Le Monde.

L'ambivalence est au cœur de la relation qu'entretiennent les Français avec la science. Les sondés considèrent majoritairement (78%) que « la science et la technologie apportent des solutions aux problèmes que nous rencontrons au jour d'hui ». Un nombre croissant (62%, six points de plus

qu'en 2011) pense qu'elles permettront aux générations du futur de vivre mieux. Mais ils sont autant à estimer que notre société devient « trop dépendante » des avancées scientifiques et techniques.

Intérêts financiers

Dans une période marquée par les scandales sanitaires et environnementaux, la proportion de Français ayant le sentiment que les scientifiques sont efficacement contrôlés par les autorités de sûreté nationale et européenne s'érode : elle était de 63% en 2011, elle est aujourd'hui de 57%.

Mais la question était peut-être mal posée : dans nombre de ces affaires, il apparaît que les autorités sanitaires elles-mêmes ont pu connaître des défaillances, et les liens entre expertise et industrie sont mis en cause.

La problématique du conflit d'intérêts, réel ou supposé, est au cœur de la confiance accordée aux chercheurs. Il est frappant de constater que les désaccords

entre scientifiques sont perçus par 46% des sondés comme motivés par la défense d'intérêts financiers privés, et non en raison des contraintes liées dans les résultats de la recherche.

Une même proportion de gens estime que les chercheurs ne diraient pas la vérité « si leurs recherches pouvaient avoir des répercussions sur la santé des individus ». 62% pensent qu'ils se laissent influencer par des groupes de pression industriels. Sans grande surprise, le nucléaire et les OGM restent les domaines où la confiance dans les scientifiques est la plus faible.

Les projets de gouvernement, qui ont tenté d'avancer les partenariats public-privé et les traités entre les deux mondes, accentueront-ils le sentiment que la recherche publique est sous-influencée, et érodent-ils encore la confiance qu'ils mettent dans les chercheurs ?

Par ailleurs, le sondage révèle que les Français se font une idée très optimiste de la place de la France dans l'artère mondia-

le : si on leur demande de nommer les pays les plus dynamiques en termes de recherche, la France arrive au second rang toutes réponses confondues derrière les États-Unis. En réalité, le pays se classe au sixième rang en termes de pair de publications scientifiques, et en milieu de peloton dans les pays de l'Organisation de coopération et de développement économiques (OCDE) pour la part de l'investissement en recherche et développement rapportée au produit intérieur brut (PIB).

En période d'austérité budgétaire, il y a peu de chances que cette situation évolue favorablement. La encore, entre le sentiment de déclassement partagé serendite dans le monde de la recherche française et le cocoon implicite des sondés, le hiatus est perceptible. ■

Hervé MORIN

Forum Science, recherche et société, jeudi 23 mai, Collège de France, Paris 5. Programme et inscription : www.forum-sc.com

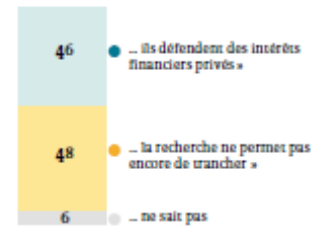
2013 poll: French citizens confident in Science but less in scientists

See also US Pew Research Center data (2015)...

sondage exclusif

... cependant, nombre d'entre eux mettent en doute l'impartialité des scientifiques...

« Aujourd'hui, quand les scientifiques ne sont pas d'accord entre eux sur un même sujet, c'est parce que souvent... »



... et près des deux tiers pensent qu'ils sont sous influence des industriels

« En France, on peut faire confiance aux scientifiques pour dire la vérité si jamais certaines de leurs recherches pouvaient avoir des répercussions sur la santé »

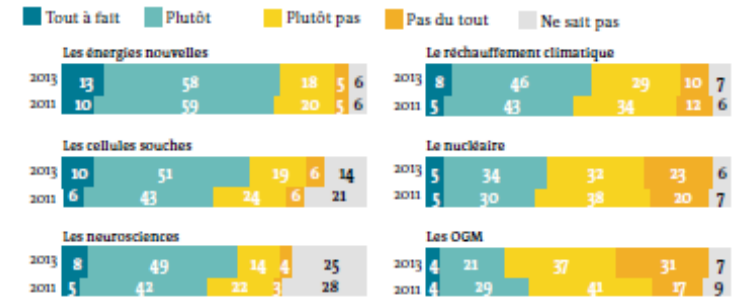


« Les scientifiques français sont globalement indépendants et ne se laissent pas influencer par des groupes de pression industriels »



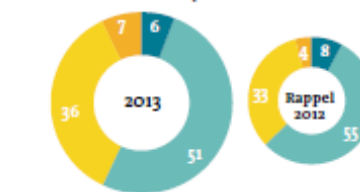
Cette défiance s'exprime surtout à l'égard du nucléaire et des OGM

Faites-vous confiance aux scientifiques pour dire la vérité sur les résultats et les conséquences de leurs travaux ?



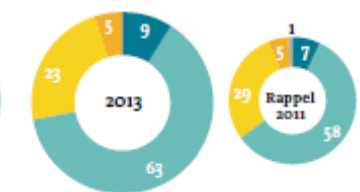
Les Français mettent davantage en doute l'efficacité des instances de sûreté pour contrôler les scientifiques

« Les scientifiques sont aujourd'hui efficacement contrôlés par les autorités de sûreté nationales et européennes »



Pour autant, ils continuent à faire confiance aux scientifiques pour effectuer leurs recherches dans un cadre légal

« On peut faire confiance aux scientifiques pour respecter les lois et les règles qui encadrent leurs recherches »



2017 poll: French citizens confident in science but concerned by applications

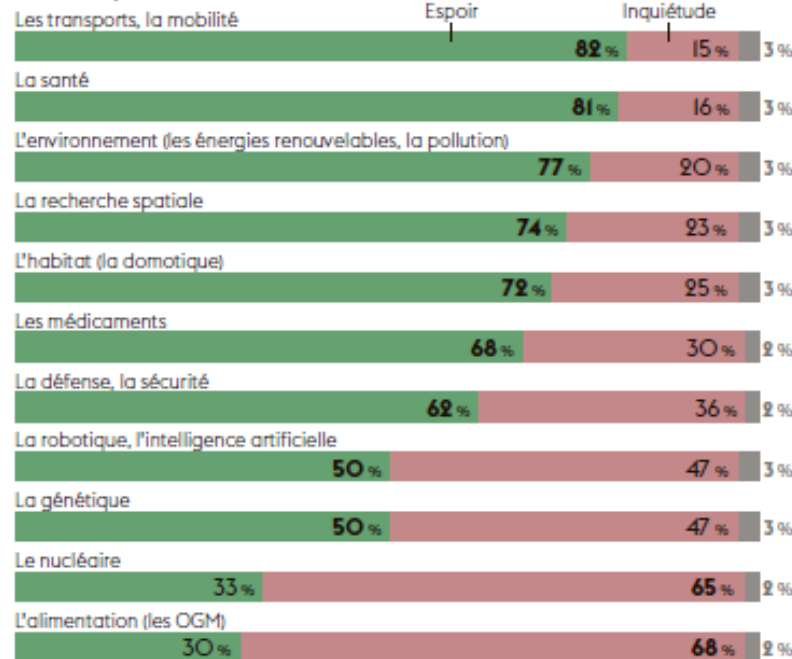
LES FRANÇAIS ET LA RECHERCHE, UNE HISTOIRE DE CONFIANCE

UNE BONNE OPINION DES FRANÇAIS SUR LA RECHERCHE SCIENTIFIQUE



UNE SOURCE D'ESPOIR, QUI SUSCITE AUSSI DES INQUIÉTUDES

La recherche dans chacun des domaines suivants suscite votre espoir ou vous inquiète ?

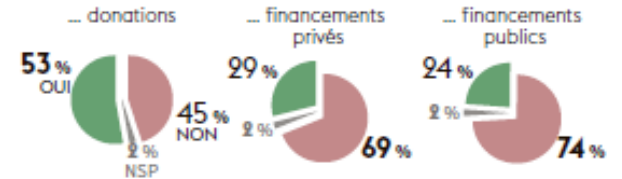


Sondage effectué du 20 et 22 septembre 2017, auprès de 1 059 personnes, âgées de 18 ans et plus, interrogées par questionnaire auto-administré en ligne.

SOURCE : OPINIONWAY POUR QUATTROCENTO « REGARDS ET ATTENTES DES FRANÇAIS SUR LA RECHERCHE SCIENTIFIQUE »

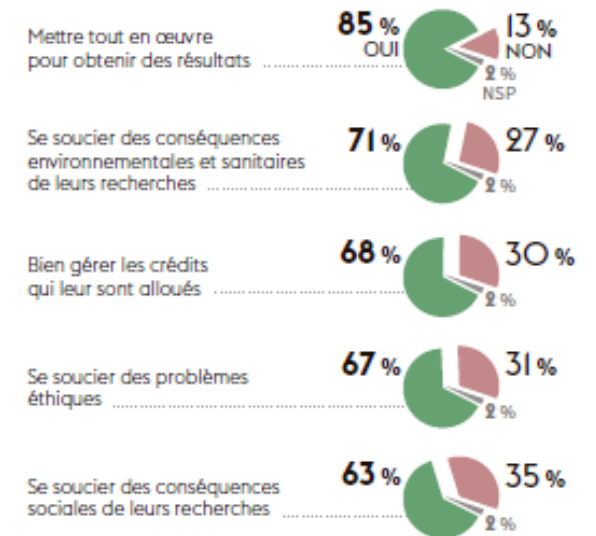
DES FINANCEMENTS JUGÉS INSUFFISANTS

Estimez-vous que la recherche en France bénéficie de suffisamment de ?...



UN LARGE CRÉDIT ACCORDÉ AUX SCIENTIFIQUES

Faites-vous confiance aux chercheurs pour ?...



Les scientifiques jouissent encore d'une cote d'amour enviable auprès des Français : 88% ont une bonne opinion des chercheurs – loin devant les politiques ou les journalistes. Mais les jeunes générations semblent plus dubitatives

quant à leur capacité à prendre en compte les conséquences environnementales et les problèmes éthiques liés à leurs recherches. Ce sont là quelques-uns des enseignements d'un sondage OpinionWay réalisé pour Quattroceto,

sur les « Regards et attentes des Français sur la recherche scientifique ». Si les filières scientifiques connaissent une désaffection, deux tiers des sondés recommanderaient à leurs enfants de s'orienter vers ce secteur. Source ma-

jeure d'espoir pour les transports ou la santé, la recherche inquiète quand il s'agit du nucléaire ou des OGM. La génétique et l'intelligence artificielle sont à la frontière entre espoir et défiance. ■

HERVÉ MORIN

Altogether, these polls' results explain why communicating corporates about GMO or any controversial applications and their supporting scientists are referring only to science and avoid talking about technical 'details'.

GMOs in brief

GMO definition: 1990/220 then 2001/18 directives (90/219 then 98/81)

- (1) "organism" means any biological entity capable of replication or of transferring genetic material;
- (2) "genetically modified organism (GMO)" means an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination;
- Within the terms of this definition:
 - (a) genetic modification occurs at least through the use of the techniques listed in Annex I A, part 1;
 - (b) the techniques listed in Annex I A, part 2, are not considered to result in genetic modification;

Impact of the GMO status

- Several GMOs (e.g. obtained through somaclonal variations) are exempted of their status implications,
- GMOs dossier of sanitary and environmental risk assessment...
 - Cost (supposed high but have a look to the CIMMYT study),
 - Reliability,
 - Locally adapted (e.g. about NTO),
 - Detection and quantification methods to be provided and interlaboratories validated, for labeling (consumers' choices),
 - Supply chains', including production fields, coexistence measures,
 - Specific and general surveillance mechanisms for monitoring foreseen and unexpected issues,

Risk assessment of GMOs in France

- 1998: Conference of citizens with a guidelines and recommendations' outcome,
- CGG (confined use) and CGB (deliberate release in the environment) administrative Commissions,
- Grenelle de l'environnement (2008)
- 2009-2014 HCB (Haut conseil des biotechnologies)
 - Scientific committee
 - Economics, Ethics and Social committee (stakeholders, Parliament representative, 3 personalities [economics, legal issues, sociology])
- 2015-2019...

A former British experience of stakeholders' involvement

Anses involvement in sanitary assessment after its establishment

Most of the risk assessment is based on corporates' data

No experts' elicitation procedure but numerous attempts to discard any dissent

Staff = molecular biologists, no environmentalist

GMOs, “hidden GMOs” and NBT

- GMOs as issued from transgenesis,
- ‘hidden GMOs’ as defined by NGOs (e.g. imidazolinone *Clearfield*[®] sunflower and soybean), issued from e.g. double haploid canola
- NBT since 2007
 - Zinc finger nuclease technology (ZFN1-ZFN3) + TALEN+ meganucleases (Crispr-endonuclease introduced after 2012)
 - Oligonucleotide directed mutagenesis (ODM)
 - Cisgenesis/ Intragenesis vs. Transgenesis
 - RNA-dependent DNA Methylation (RdDM)
 - Grafting (GM rootstock / scion)
 - Agro-infiltration (Agro-infiltration “*sensu stricto*”, Agro-infection, Floral-dip i.e. plant transformation)
 - Reverse breeding
 - Synthetic biology (abandoned later on as still undefined)

A gibberish of unrelated, misleading people, techniques, old and new, renaming and mixes affecting genome, epigenome and epitranscriptome

European WG 2007-2012 with a final report not publicly released

Expertise in theory:

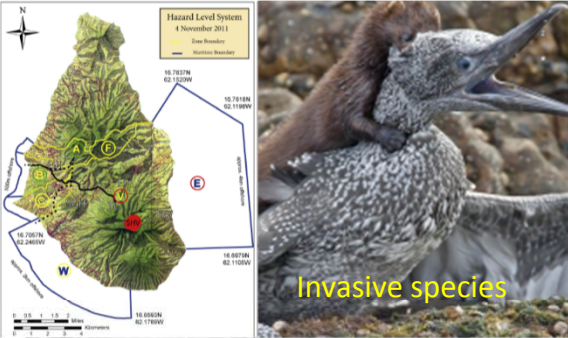
enlightening the public Authorities to make appropriate decision toward the common good

But what is the common good?

From the satisfaction of some shareholders to consumers and producers' wishes...

Understanding causality and uncertainty in volcanic observations: An example of forecasting eruptive activity on Soufrière Hills Volcano, Montserrat

T.E. Sheldrake^{a,b,*}, W.P. Aspinall^a, H.M. Odbert^a, G. Wadge^c, R.S.J. Sparks^a



THE POWER OF BIAS IN ECONOMICS RESEARCH*

John P. A. Ioannidis, T. D. Stanley and Hristos Doucouliagos

We investigate two critical dimensions of the credibility of empirical economics research: statistical power and bias. We survey 159 empirical economics literatures that draw upon 64,076 estimates of economic parameters reported in more than 6,700 empirical studies. Half of the research areas have nearly 90% of their results under-powered. The median statistical power is 18%, or less. A simple weighted average of those reported results that are adequately powered (power $\geq 80\%$) reveals that nearly 80% of the reported effects in these empirical economics literatures are exaggerated, typically, by a factor of two and with one-third inflated by a factor of four or more.

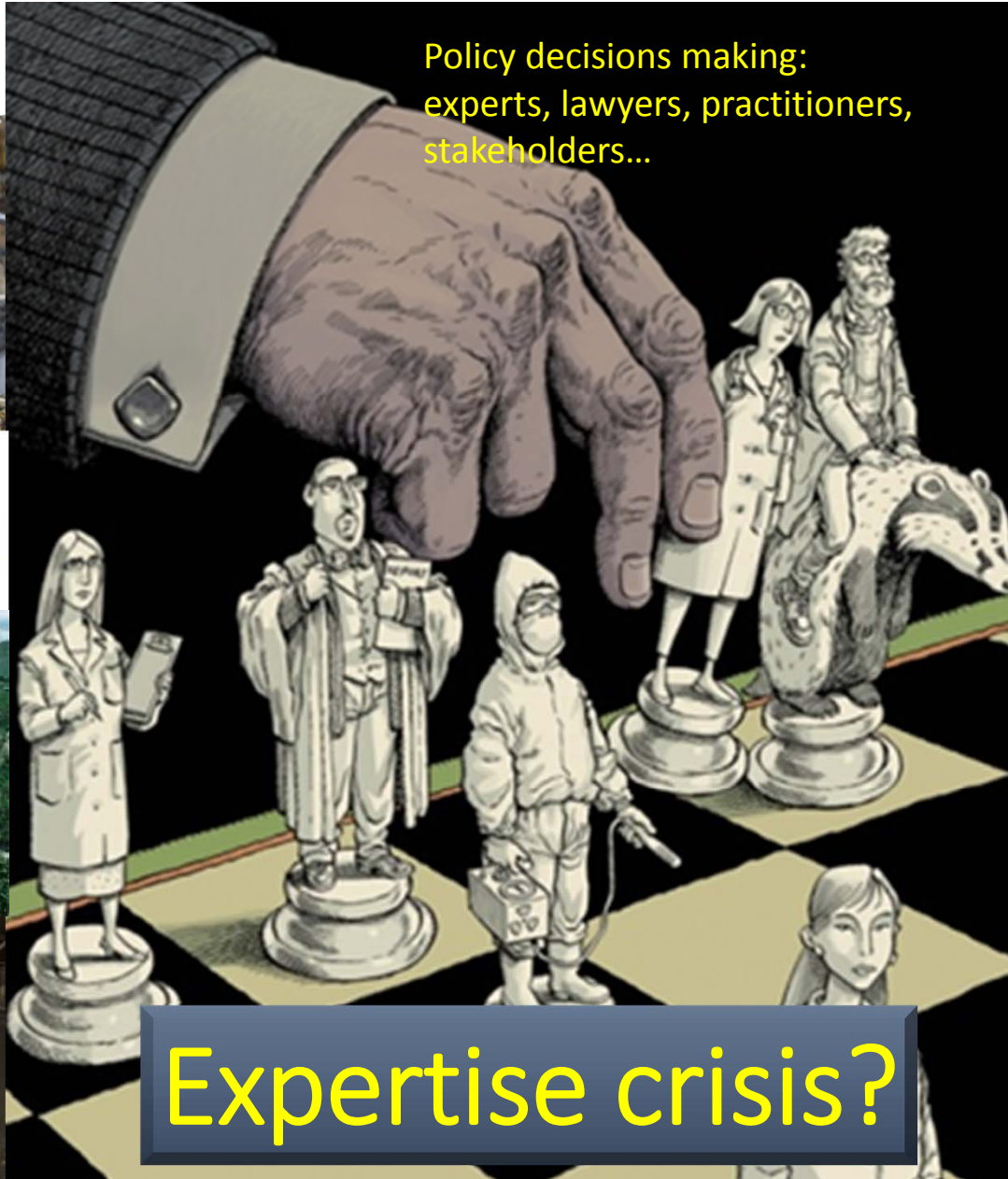


River management: dams' erections and leveling



Urbanization densification and flooding risks

Policy decisions making: experts, lawyers, practitioners, stakeholders...



Expertise crisis?



Italy earthquake experts charged with manslaughter

Risks commission members to face trial over failure to give sufficient warning about L'Aquila earthquake in 2009



Smog / air pollution

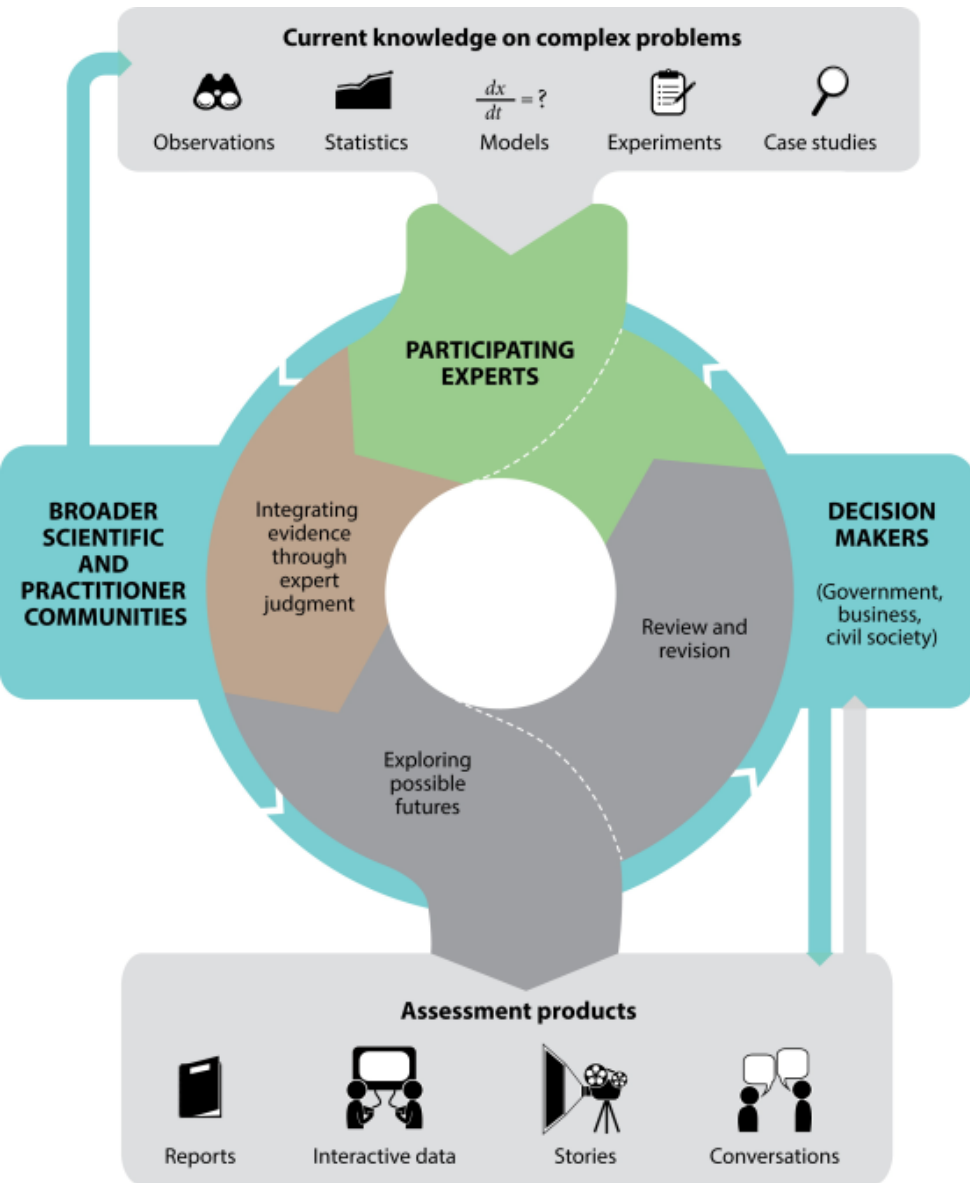


Playing on an iceberg



Worst decision EVER

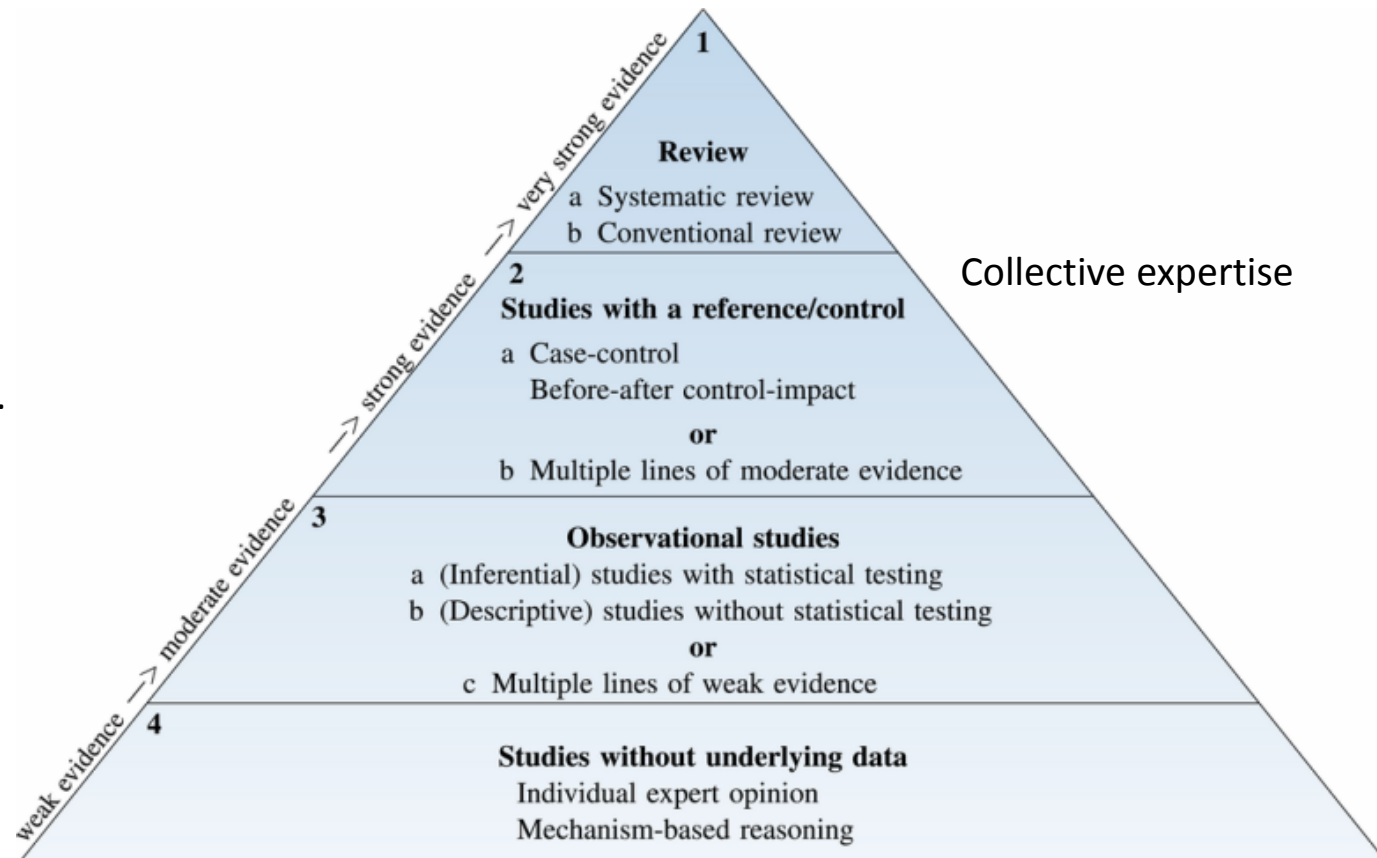
Uncertainty assessment and risk management in decision making



- People not always rational but proficient,
- Context-bound modeling vs. context-free,
- Process-orientation vs. prediction of outcomes,
- Empirical-based prescriptions,
- Experts' situation: stress, time pressure, dynamic conditions, ambiguous information, ill-defined goals,
- Minimizing biases such as cherry-picking and vote-counting,
- Appreciating the robustness of papers for meta-analyses and narration,
- **Weight of evidence** integrating plurality / dissensus and, as far as possible, reliable probabilities.

Increasing the 'weight of evidence' by decreasing the uncertainty

- Statistical uncertainty / burden of **proof** (Analytical error propagation, Monte Carlo simulations, sensitivity analyses, Bayesian, Robuste decision making...)
- Compiling scientific advice with expert elicitation by interviews, the Delphi, the Cooke's or Focus groups Decision methods, Nominal Group Technique, Q methodology, MCDA (Multi-Criteria Decision Analysis), metaanalyses, systematic literature reviews...
- Subjective judgement
- Systematic errors
- Incomplete knowledge / gaps
- Temporal variation
- Inherent stochasticity
- Decreasing experts' a priori convictions and related biases



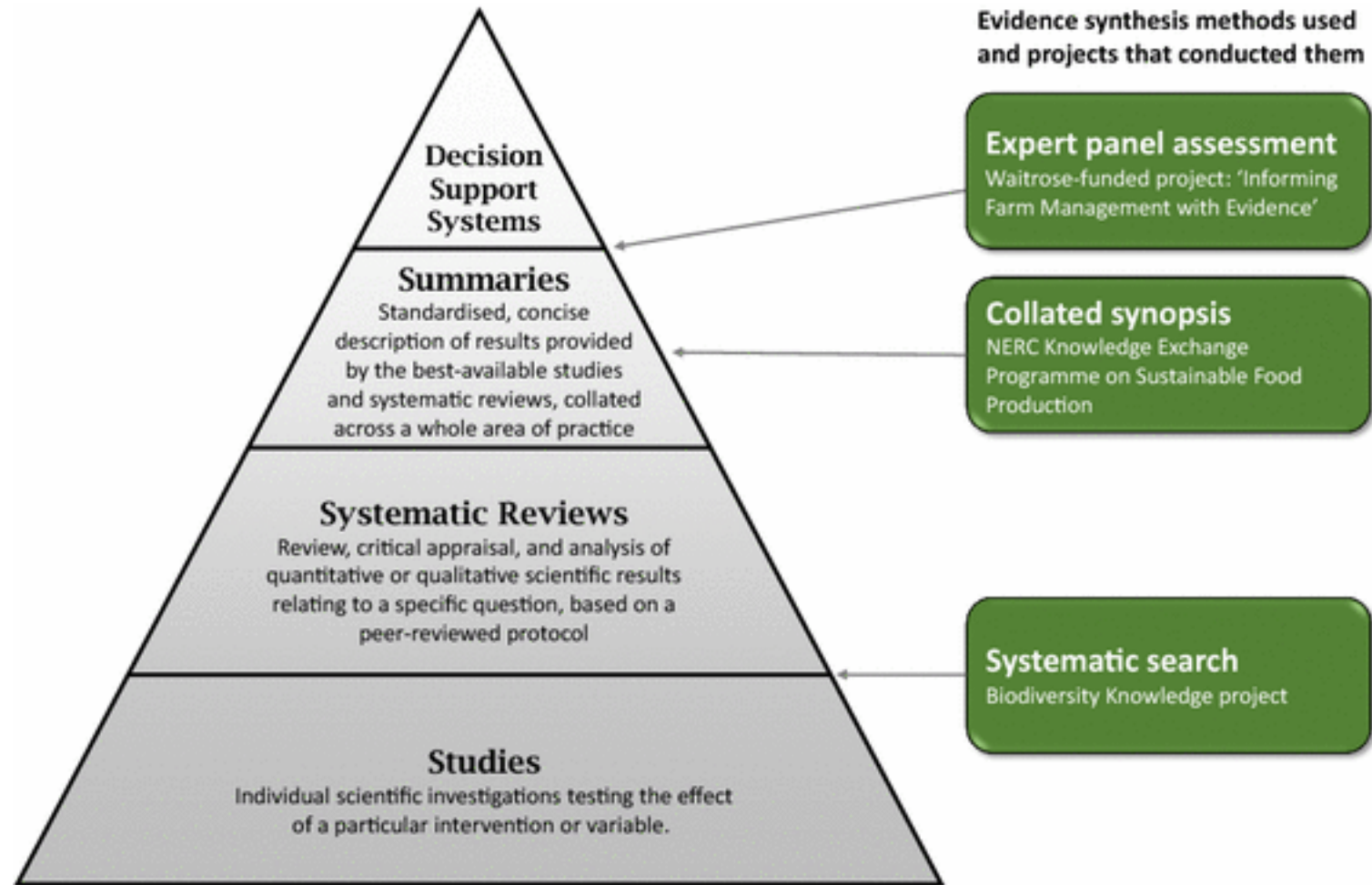
Taking decision in uncertain situations

- Explicit rationale,
- Peer-reviewed protocol,
- Systematic bias avoidance,
- Transparency,
- Conflicts of interest,
- Plurality,
- Reliability,
- Traceability,
- Stakeholders' involvement,
- Repeatability / reproducibility,
- External experts / political decision.

SLR: backdoors still present...

Usurpations (see HCB advice on a peer-review paper)...

Main concern about the citizens and NGOs' abilities to understand and prepare counterarguments...



French case study

France as a case study: NBT at the HCB and the Conseil d'Etat

- Working Group 2008-2015 without referral nor self-referral of tasks to be performed,
- December 2015: "discussion on a summary note" of the WG
 - No gvt referral nor self-referral, thus without precise request of work to be performed,
 - "Written in a weekend or so",
 - provided to the Scientific Committee 3 working days before the HCB SC meeting,
 - with less than a third of the final document (remainder to be provided later on),
 - with regulatory and economic considerations of the CEES but not of the CS,
 - provided to CEES the same day (contrary to the procedures' scheme),
 - which will be announced the days after as to be provided as a notice to the government,
 - request for dissent refused: resignation of a SC scientist then several stakeholders of the CEES.
- Communication "double talk" to justify a misuse of procedures,
- Resignation of the CS: an expert *intuitu personae* vs. organizations of the highest quality,
- Status of the document regressed several times on the HCB website but was always presented by the gvt as a "advice" of the HCB,
- Request to the gvt to urgently provide the HCB with an official referral on NBT,
- New SC WG on NBT started in 2016 for writing a new CS document... delivered November 2017 despite a new dissent,
- Ad-hoc working group ('coach', chairs and staff) i.e. a judge and party WG on HCB governance. Conclusions after several months: the rules of procedures have to be applied, the documents have to be provided in due time, procedures have to be transparent, minority opinions have to be taken into account as stated by the procedures...

France as a case study: NBT at the HCB and the Conseil d'Etat

HCB:

- After a clear lack of reflection on how to organize the scientific expertise,
- Some stakeholders deceived by the CEES as present for co-management of GMOs issues,
- After the resignations: “business as usual” to be compared to the same issue of dissent for an Anses’ expertise of several years and its professional ethics committee,
- No consequence for the HCB governing board despite the non-compliance of tendering rules, as stated in the conclusions of the ad-hoc group.

‘Hidden-GMOs’, NBT and the Conseil d’état:

- Judicial procedure in 2015 before the Conseil d’Etat by organizations against Prime minister’s decisions of “VrTH” (“hidden GMO”) approvals,
- NBT were included during an exceptional ‘investigation at the helm’ (‘enquête à la barre’, June 2016),
- The Conseil d’Etat then sent several preliminary questions to the European Court of Justice (ECJ),
- ECJ General advocate comments delivered on February 2018...

After the GMOs, the NBT:
biased semantic and rhetoric battles
to mask the financial goals

NBT: some general considerations

- A series of agricultural technical evolutions, often improperly described as 'revolutions' (as for middle-age, green...),
- A technical evolution of molecular biology: GMOs, then NBT, synthetic biology,
- Related techniques: cooking recipes that have been used for several decades generating mutations and epimutations (see the London's October 2016 seminar)
- Techniques used without evaluation guidelines on certain impacts (e.g. epigenome, see EFSA symposium, June 2016) nor an appropriate quality assurance scheme,
- Societal issues that led to the refusal by citizens of certain techniques and leading to regulatory questions (what is mutagenesis, GMO or not, exempted or not?) being processed at the level of the ECJ,
- A society where technical progress and innovation are asserted as a source of happiness and wellbeing by both private and public actors (ministries in charge of the environment and agriculture, CTPS vs. Evaluation agency ...)

What can be learned from the current NBT controversy (ZFN, TALEN, Crispr-nuclease) and other techniques (negative segregants, RdDM, RNAi, OdM, grafting ...), copy / paste errors, positions of experts and authorities they control, business lobbies and policies?

NBT : rhetoric and omerta

- Exaggerated cost of the corporates' dossier compiling (see the CIMMYT case study on GMOs),
- Confusing copy-paste, without any updating or critical thinking, among numerous documents, ex:
 - the story of the definition of *recombinant DNA* and the nucleotides,
 - Traceability / detection / identification, from the industry arguments to the European SAM report,
- From flooding of promises reminiscent of GMOs and cloning promises 30 and 20 years before, with many omissions: breeding acceleration, feeding the world... to a fabulous world 2.0 without genetic diseases nor harmful organisms, around precision medicine,
- An abuse of undefined wording such as 'natural' (e.g. use of natural mechanisms such as NHEJ, but current GMOs also use natural DNA repair mechanisms), a semantics of fight ('new' synonymous with breakage for patents, and 'plant breeding / selection' for falling asleep citizens), 'editing' rather than modification, this despite the many errors, 'precision' despite several unintended effects such as off-target ...
- A focus on 'targeted mutagenesis' not mentioning the unexpected effects of old techniques (protoplastisation, regeneration of plants...) used to generate mutations and new techniques of genome modifications,
- A mechanistic presentation of the 70s-80s of the genome and molecular biology instead of the current one of dynamic networks constantly interacting between genomes of a cell, between cells, between tissues,
- A biased choice of mechanisms and of their relative importance e.g. RdDM (a way of obliterating the problem of gene regulation, pleiotropy...):
 - 'Methylation of DNA as a natural process',
 - 'Unmodified DNA sequence' ...,
- A mix of confusing situations: old reassuring techniques such as grafting but with GM rootstock without consideration of the remote effects on the scion and its products ...
- Confusion maintained for example by the different definition between countries about e.g. agro-infiltration (agro-infection itself and floral-dip included or not),
- A flooding of patents covering mostly insect resistance and herbicides tolerance traits, not satisfying consumers needs,
- Gibberish confusion with 'concepts' (e.g. cis-, intra- and trans-geneses using the same techniques) presented at the same level as techniques.

A semantic battle and biased rhetoric to mask the financial goals

The effective expertise framework

Who's expert in which context?

- As a kid, you can be the expert for the bicycle of your sister,
- Administrations' delegates: OECD, EC's committees... with several instructions,
- As a "connoisseur", such as a scientist or as stakeholders' representative...

But

- Experts are generally chosen through non transparent procedures despite the official calls,
- There are no efficient career award or earning motivations, as shown by several reports, for young experts, whatever the work quality,
- Several 'experts' are collecting nominations as corporate administrators are collecting attendances fees,
- Experts are themselves "politicians" influenced by their training, networks and opinions (as the scientists in their labs) with different opinions and strategies, hidden agendas...
- Experts may be rare, difficult to mobilize, particularly in controversial areas, possible biases in their choice by e.g. the nominated chairs...
- Experts are generally questioned about unstable situations, with large uncertainty margins, affecting different possible scenarios, sometimes with guidelines and norms (e.g. toxicology) not taking into account recent research data...
- Expertise can be also mostly based on stakeholders documents (expertise privatization?) without power of initiating additional research, in very short expertise timing,
- The quality of expert's work is generally not assessed (some are just making summaries instead of applying critical mind or checking the application of legal directives), nor bad job sanctioned,
- Generally highly depending on the secretariat competence, a staff whose members can publish to express their viewpoints (see e.g. EFSA's staff) and thus influence the experts.

The experts / politicians relationships

- The enlightened prince, a kind of epistocracy,
- The empire of standards: the legitimacy of “science based” and the full epistocracy. Which expert to choose and who is nominating them through which non transparent procedure?
- The technical democracy: the power of experts decreases, citizens are involved (consensus conference, HCB CEES...). But who is representing? Several limits (see the debate about nanotechnologies in France).

Direct interferences during the expertise

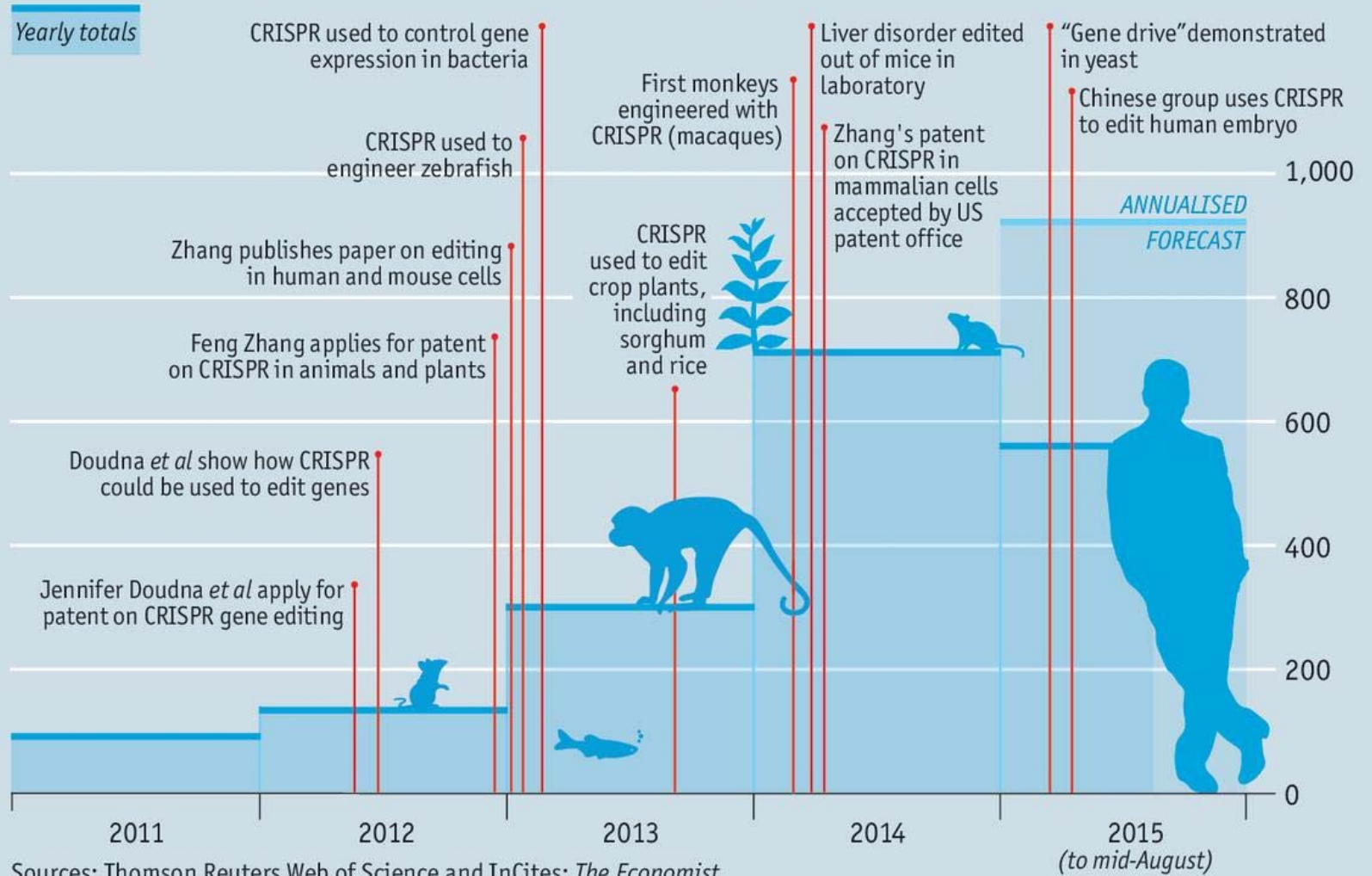
- Social pressures of an economy of promises:
 - Colleagues' interventions about e.g. socio-economic impacts (feeding vs. nurturing the world, children's nutritional deficiencies, supposed huge costs of approval dossiers...),
 - Nationalist arguments: agricultural exportations and trade balance, improving competitiveness, Shanghai's ranking of our research,
 - Authority arguments during colleagues' interventions about what "everybody knows", tribunes of renowned scientists of other domains,
 - The usual and intentional confusion between science and their applications,
 - Number of "successful publications" (forgetting the fashion effect, the funding needs with claims for disruptive technics, the publication and votecounting biases...)
 - No compliance to scheme rules (e.g. CS HCB meeting on dec. 16, 2015 and following steps) and their control (internal WG's conclusions: to respect the rules of procedure, be transparent, provide documents in time...), independent structure without ethical committee at the difference of Anses professional ethics Committee (recent dissensus issue)

**In conclusion: the red Queen race of Alice in Wonderland
The Promethean myth**

A self-fulfilling prophecy

Stepping up

Number of CRISPR papers published and some research highlights



Sources: Thomson Reuters Web of Science and InCites; *The Economist*

Economist.com

Crispr-endonucleases:
fashion and new
opportunities of
funding...

And the bias of
publications (as for
cloning 20 years ago...)

As for the 80% of new products withdrawn from retailers' shelves, the enthusiastic predictions of experts based on corporates promises are often disconnected from the day-to-day realities.

e.g. vitamin C content and flavors of the unoxidized Artic® apple?

Economic interest for the producers currently overproducing apples?

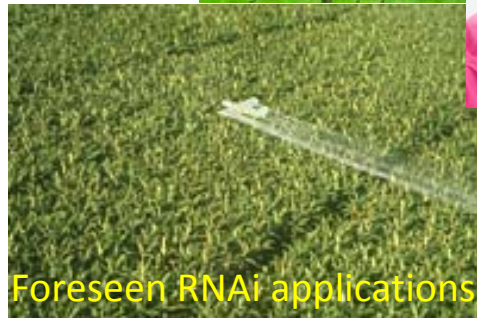
Products may not 'fit the times' as for instance local productions



Conventional Apple Variety



Arctic® Apple Variety



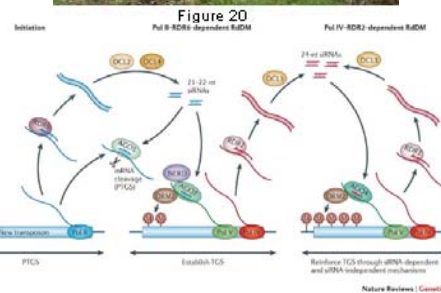
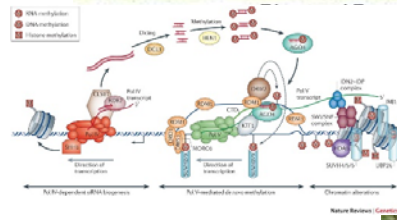
Non-Bt Eggplant



Bt Eggplant



A comparison of corn with disease and Bt corn.(Photo by Biotech info center)



Beside the 'Frankenfood' effect, are consumers, but also supply chains, really wishing such changes?

An economy of promises and a race of lies

Genta: 1998-2012

The strange but true tale of a beleaguered
with 100 quadrillion shares outstanding.



Fraud and misconduct in science: the stem cell seduction

Implications for the peer-review process

What pushes scientists to lie? The disturbing but familiar story of Haruko Obokata

The spectacular fall of the Japanese scientist who claimed to have triggered stem cell abilities in regular body cells is not uncommon in the scientific community. The culprit: carelessness and hubris in the drive to make a historic discovery

theguardian

Breakthroughs IN BIOSCIENCE

Une start-up d'analyses sanguines soupçonnée d'avoir menti sur sa technologie

Par Anais Cheriff <http://www.liberation.fr/auteur/16518-anais-cheriff> — 19 avril 2016 à 17:18



N° 2198
ASSEMBLÉE NATIONALE
CONSTITUTION DU 4 OCTOBRE 1958
ONZIÈME LÉGISLATURE
Enregistré à la présidence de l'Assemblée nationale le 24 février 2000.

OFFICE PARLEMENTAIRE D'ÉVALUATION DES CHOIX SCIENTIFIQUES ET TECHNOLOGIQUES

RAPPORT

LE CLONAGE, LA THÉRAPIE CELLULAIRE ET L'UTILISATION ÉMERYONNAIRE DES CELLULES ÉMBRYONNAIRES

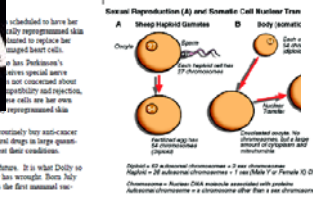
PAR M. Alain CLAEVYS, Sénateur, et M. Yves CHAUVIN, Député.



Cloning: Past, Present, and the Exciting Future

by Marie A. Di Berardino, Ph.D.

...distant... recently cloned from an adult cell, one takes this as a sign of a new era in cloning. The process that produced Dolly differs from ordinary reproduction in one major way. From body cells, the cell's nucleus and the cell's DNA, which is the genetic blueprint for an individual. The process that produced Dolly differs from ordinary reproduction in one major way. From body cells, the cell's nucleus and the cell's DNA, which is the genetic blueprint for an individual. The process that produced Dolly differs from ordinary reproduction in one major way. From body cells, the cell's nucleus and the cell's DNA, which is the genetic blueprint for an individual.



Drug giants turn their backs on RNA interference

A once much-touted technique faces a difficult transition to the clinic.

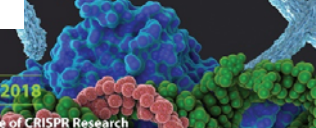
BY KEVIN LESCHNER
Not long ago a technique called RNA interference (RNAi) seemed to be the best bet for commercial success. In October 2002, scientists reported the production of specific proteins using specially designed RNA molecules, and it quickly became a favorite tool of basic research. By 2006, the excitement was such that the discovery was awarded the Nobel Prize for medicine, and the new gene-based pharmaceutical gene-silencing drugs were being tested in clinical trials. However, the excitement quickly faded as the first RNAi-based drug failed to meet its goals.



AGRICULTURE'S FIRST SINGLE-BAG REFUGE SOLUTION

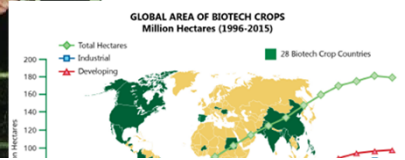
No more calculations. No more separate, structured refuge. Refuge compliance is now all farmers' shoulders — and on ours. See how Monsanto is making insect resistance management easier.

The CRISPR Journal



Debut Issue 2018
The Cutting Edge of CRISPR Research

Crispr body-built dogs



Is RNAi Dead?

Recurring theme in the way that many pharmaceutical companies approach new technologies is that they are initially extremely enthusiastic, perhaps excessively so, but then subsequently overreact in the opposite direction, abandoning them when the first humps in the road come along. Only a few years ago, the affection of big pharma for RNA interference (RNAi) seemed unlimited. Merck had acquired

Authority arguments

- Usual sentences during sessions: ‘everybody knows’,
- Appeals to authority such as chair taking the time instead of favoring the expression of diverse opinions,
- Subordinate relationship, funding or positions backlash in future e.g. call for tenders...
- Standardized risk assessment (e.g. toxicology) vs. research issued assessment (e.g. epigenetics without guidelines, effects of fed miRNA on host’s genes regulation...),
- Using several cognitive biases,
- Disqualification by politicians of experts suspected of opposition (see OPECST April 2016 online video).

Experts' integrity

- Unclear expertise aim/formulation, or referral including its own response (see. HCB request for referral in 2016 on NBT),
- Direct links of interests and earnings (merchants of doubt, funding effect...), but also having direct links with alternative solutions (e.g. CTPS representative in HCB),
- Cherry picking of publications, reproducibility crisis, lack of data confirmation (ex: Germini et al. 2018),
- Personal opinions of the experts, influencing the work, definition of the common goods,
- Biased information / communication (see the lack of explanation of the HCB CS to CEES on 'related techniques'),
- Circular reasoning (e.g. identification of NBT techniques and derived products, effects of genes modification vs. verifications....),
- As for GMOs, an asymmetry of evidence (see the recent Schaefer et al. 2017 retraction on mice's off-targets: new standard, hiding exon skipping, structural rearrangement... Vs. false positive after NBT use),,
- Lack of controls of the quality and integrity of the expertise work, sanctions.

**AN EXAMPLE OF CIRCULAR REASONING:
THE IDENTIFICATION OF THE INITIALLY USED NBT TECHNIQUES
AND DERIVED PRODUCTS**

Principle of the matrix Approach
(gathering a converging proof network)

<http://www.inra.fr/Entreprises-Monde-agricole/Resultats-innovation-transfert/Toutes-les-actualites/Detecter-les-OGM-inconnus>

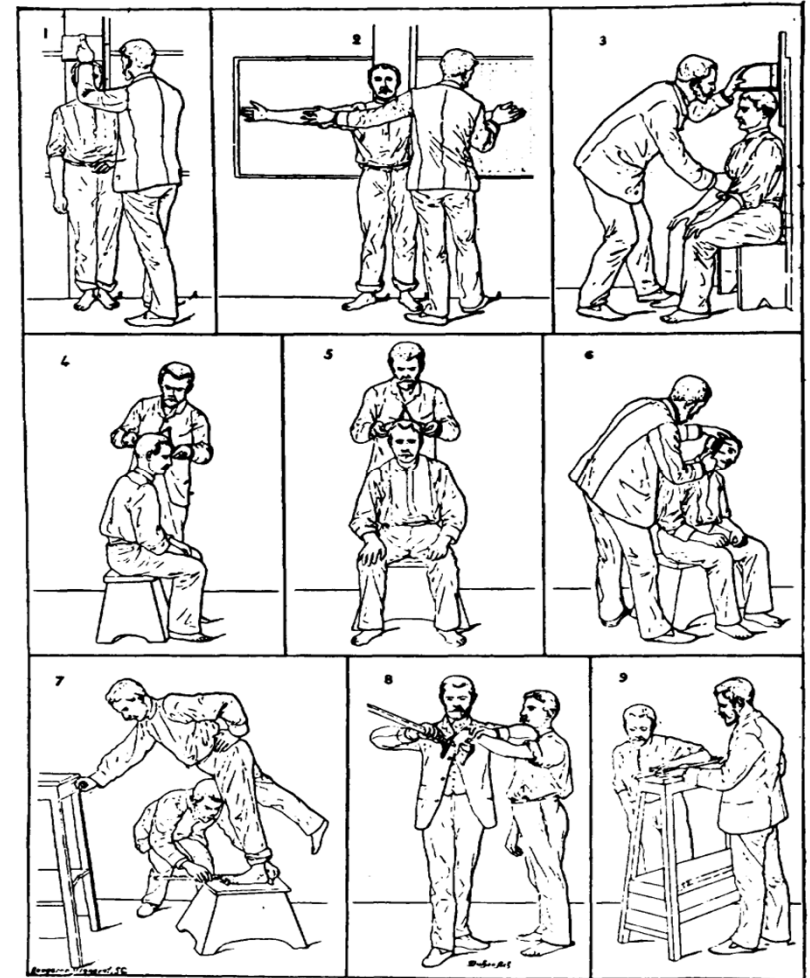
Classic premises of identification

- Principle:
 - Observe / distinguish characters, traits ... eg shape of flowers, animals, hair or feathers ...
 - Inventory the elements: locomotion devices, bone, disposition, ontogenesis ...
 - Classify the elements: phenotypic, genotypic, epigenotypic, epitranscriptomic ...
 - Analyze nucleic acid sequences; proteins, compare DNA / proteins (exon jumps, alternative splicing) ...
 - Combine the elements if necessary according to the desired degree of precision,
 - Correlate, for example in trees (evolutionary tree ...)
- Users: Aristotle, Linnaeus, Jussieu, Darwin ... breeders of seed companies ...
- The identification of NBT techniques and products is only an application of the methods and targets used in taxonomy, phylogeny / cladistics / phenetics / statistics, varietal identification, marker-assisted selection, detection of GMOs ... assisted or not by various statistical tools, databases, decision support systems (DSS) ...

Other examples Of the matrix approach

Basic principles of scientific identification as synthesized by Alphonse Bertillon in judicial anthropometry

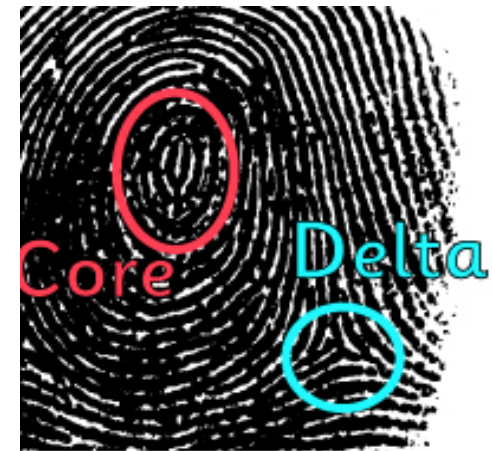
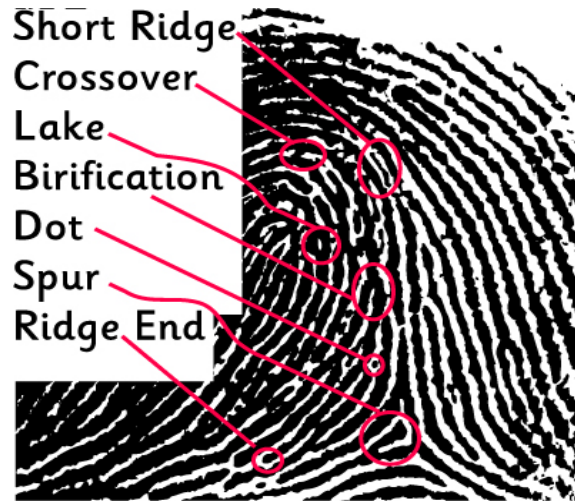
RELEVÉ DU SIGNALEMENT ANTHROPOMÉTRIQUE



1. Taille. — 2. Envergure. — 3. Buste. —
4. Longueur de la tête. — 5. Largeur de la tête. — 6. Oreille droite. —
7. Pied gauche. — 8. Médius gauche. — 9. Coudée gauche.

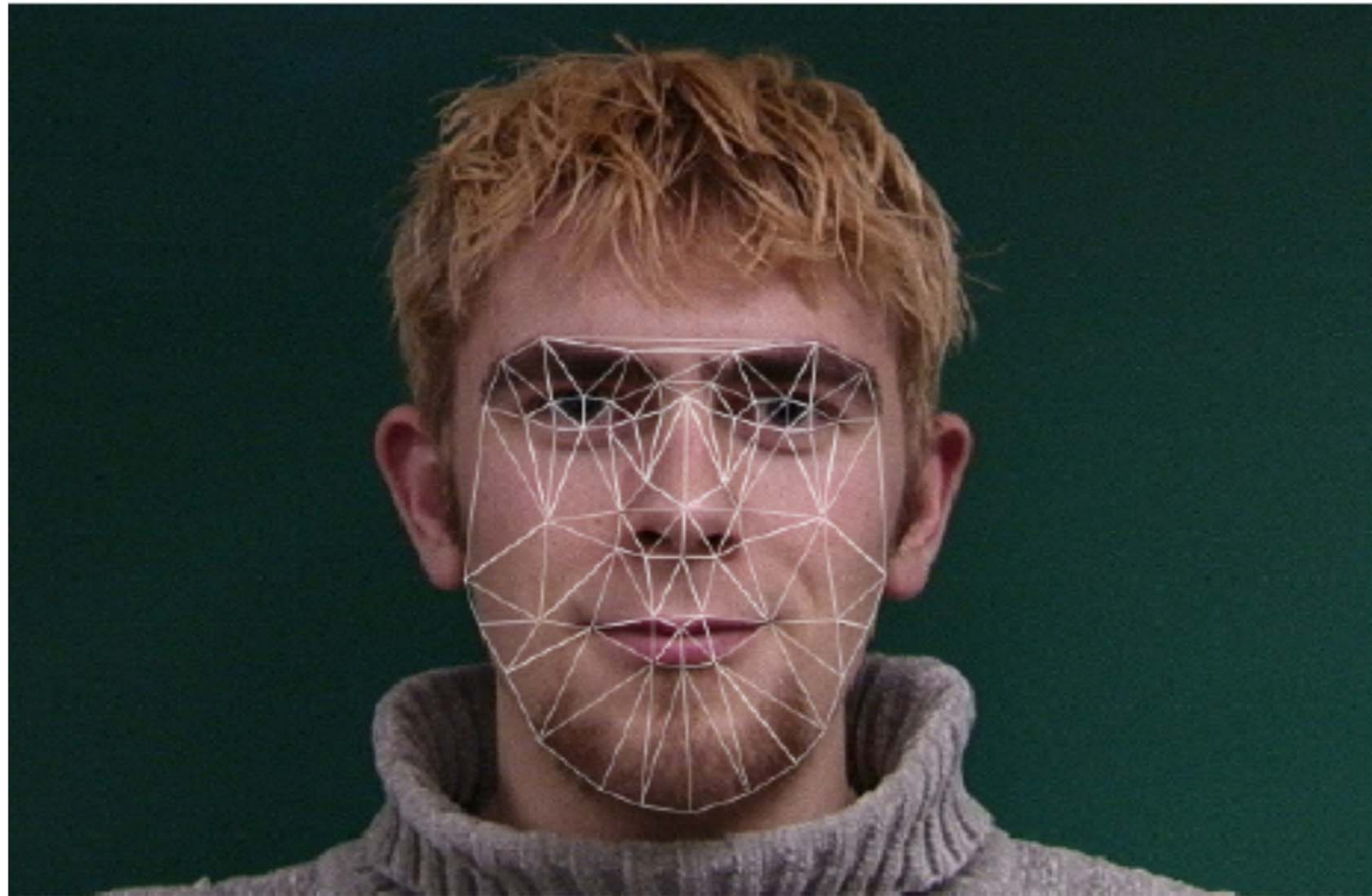
Another example of the matrix approach

Some characters / traits of differentiation in dactyloscopy



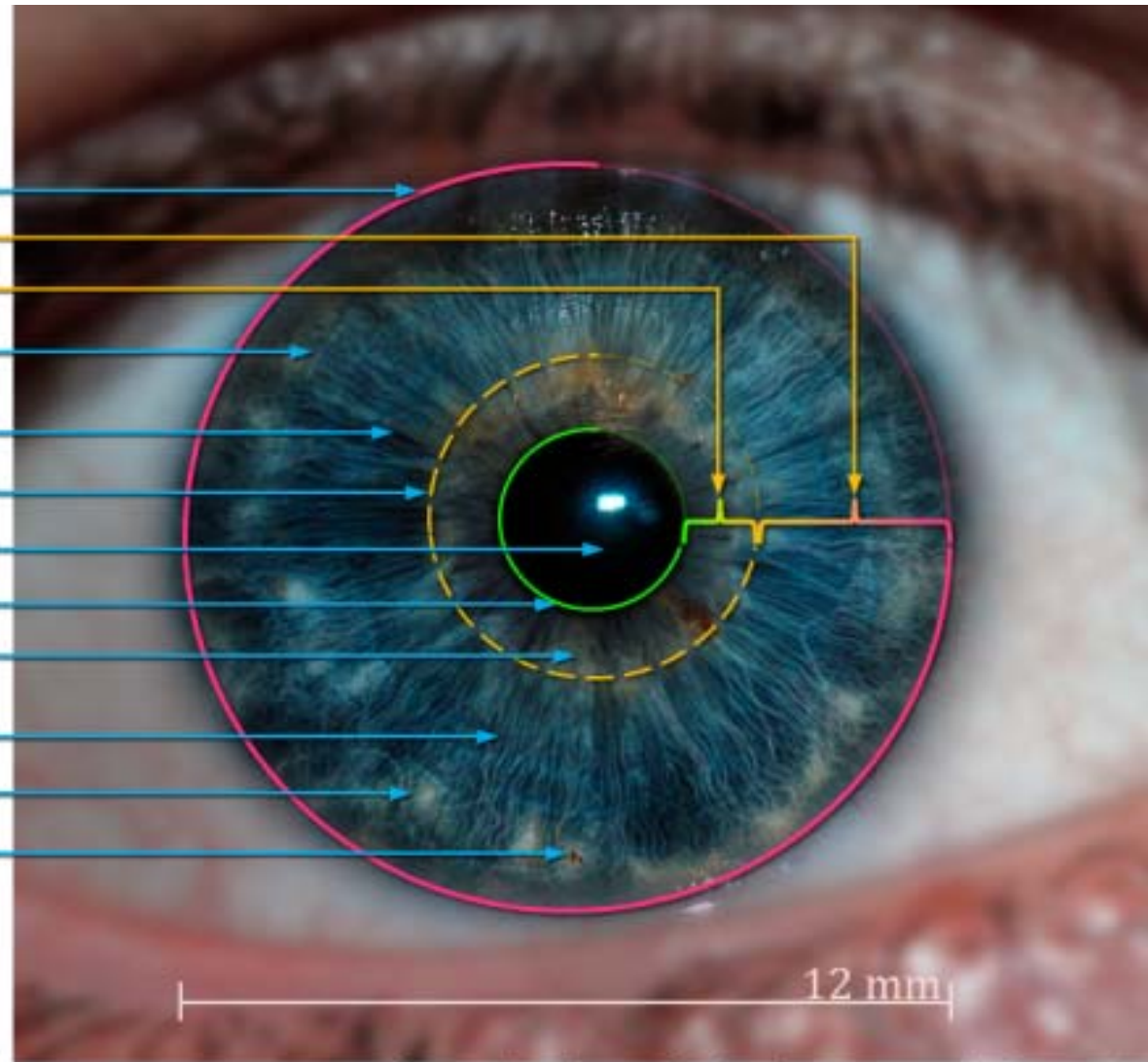
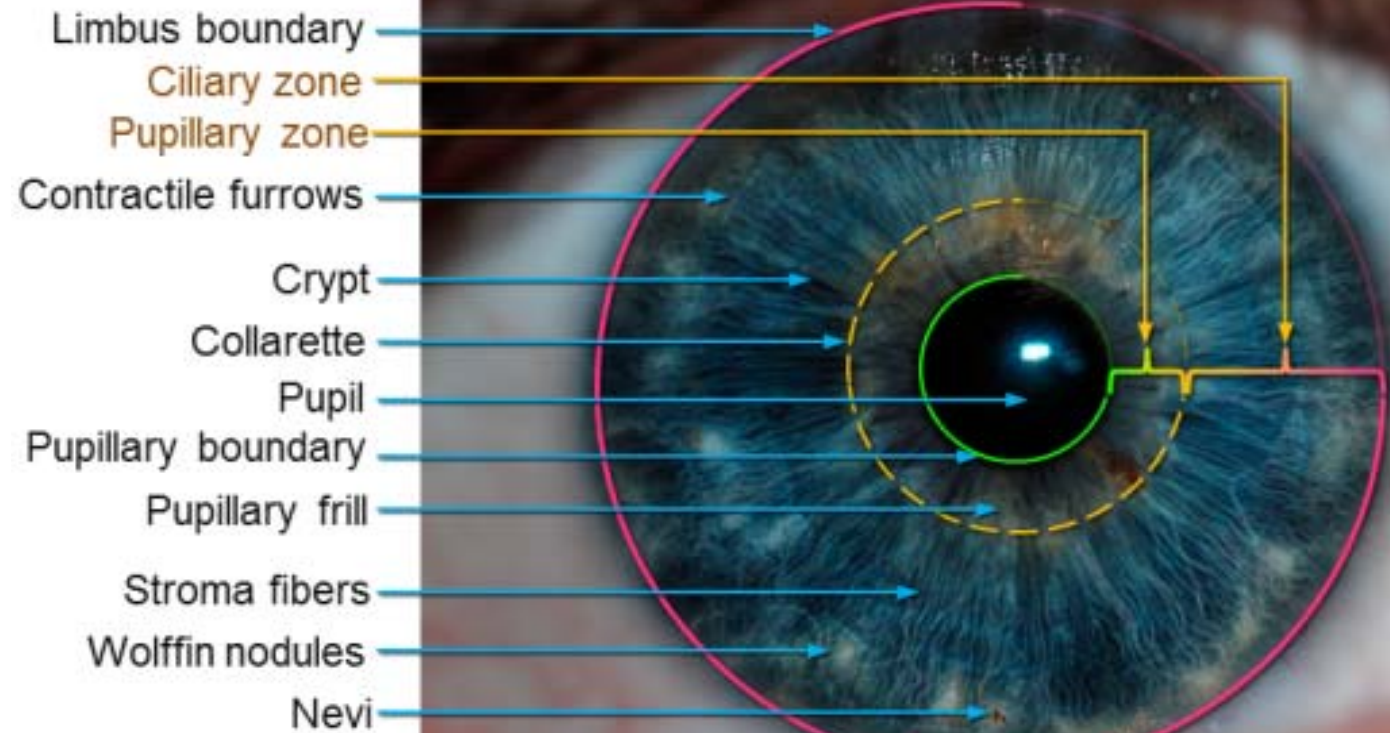
Another
example of
the matrix
approach

Multipoints
facial recognition

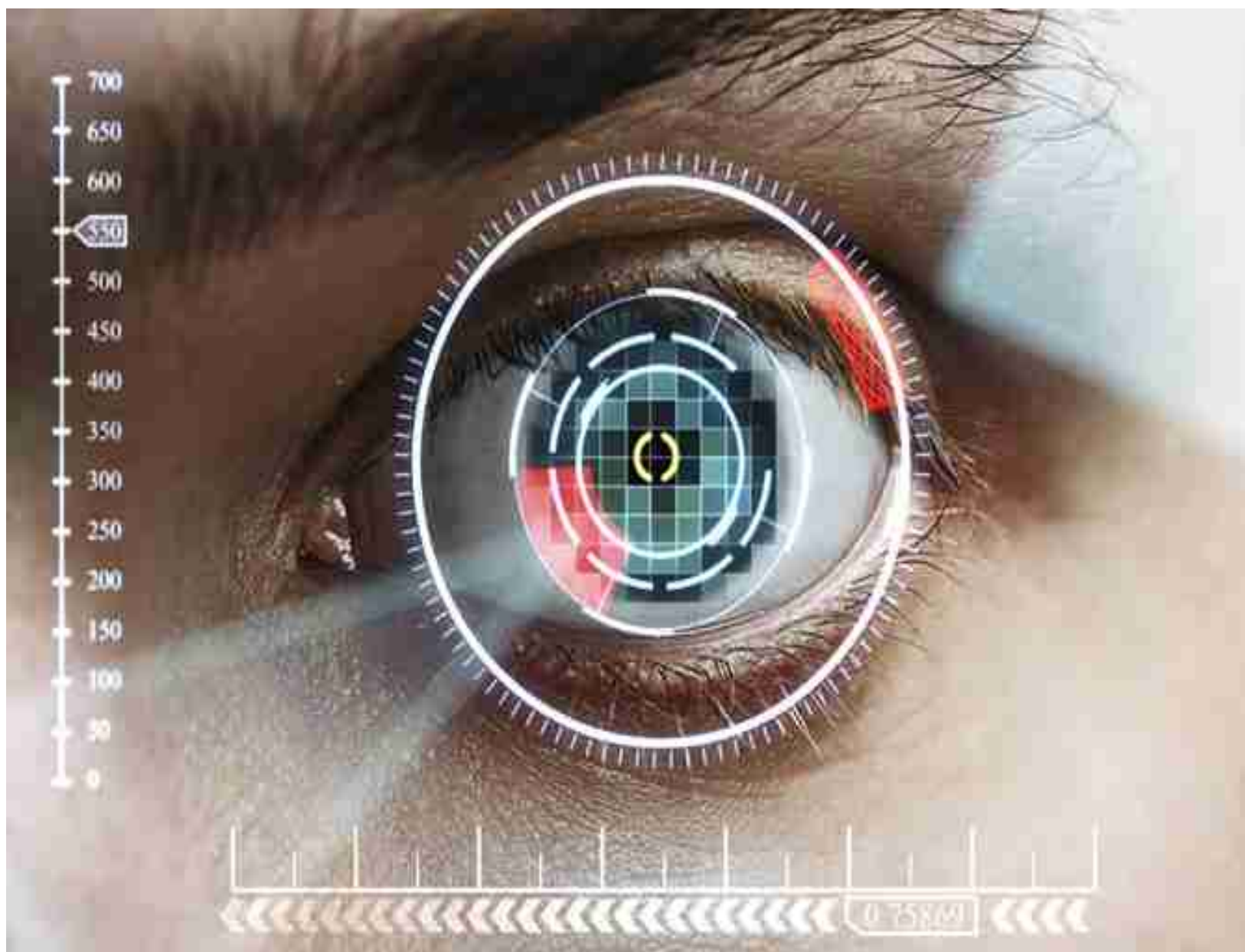


Another example of the matrix approach

Iris recognition



Source (eye image): Dr. Jan Drewes. www.jandrewes.de





Genetic polymorphism

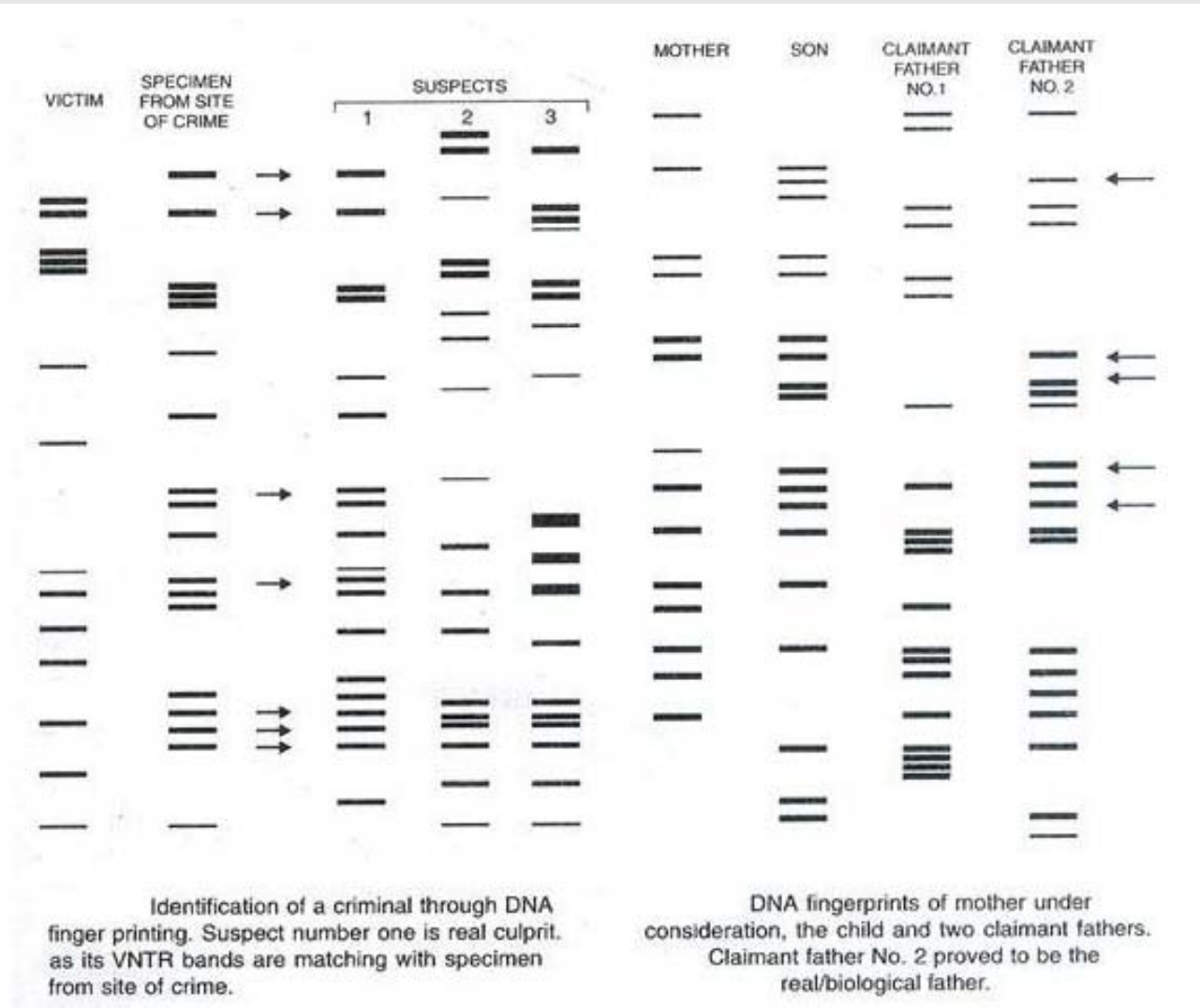
DNA Fingerprinting

How to become one of the experts of the technical and scientific police,
or - more prosaically – how to identify varieties
to do marker-assisted plant selection ...

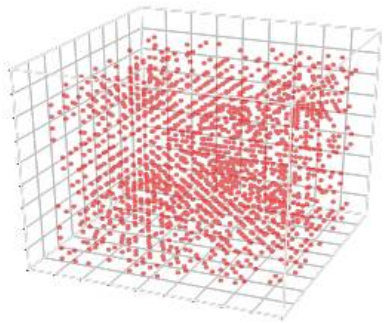
"In addition, the plant genome is extremely diverse," says Jeffrey Sander, scientist at the Pioneer Molecular Engineering (Johnston, Iowa),
"Between two varieties of corn, there is almost the same genetic distance
as between man and monkey. "

Another example of the matrix approach

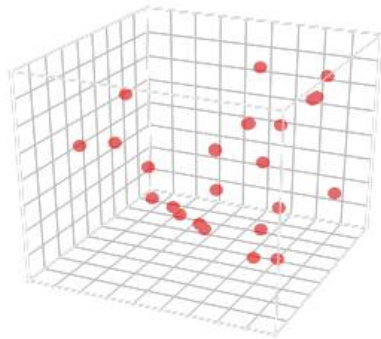
Depending on the context, the "weight of evidence" (here the number of identification bands differentiating individuals in these forensic studies) may differ ...



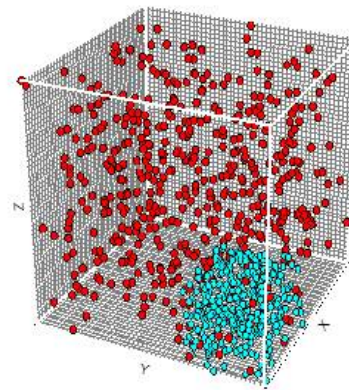
The matrix approach to identify the NBT techniques initially used and the derived products is based on the assemblies of markers of different types, for example in genomes and epigenomes



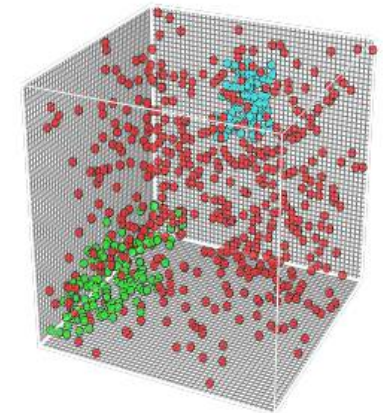
Markers in all genome and epigenomes (ex: used for a MAS, PAM, off-targets, translocation, transversion ... frequency, cartography ...)



Choice of identification markers of the species



Choice of markers differentiating products from *in vitro* techniques



Choice of markers differentiating one (of) technique(s), ex. Crispr-endonuclease (s) natural mutation (s)

- Choice of a combination for unambiguous legal identifications
- Choice of one (or some) relevant marker (eg PCR on targeted mutation-PAM) for routine detections (aspects of cost, speed ...)

Conclusion

- The circular reasoning was: the NBT mutation is supposed similar to a natural mutation, as such we cannot identify the NBT used for producing it, there is thus no identification method for distinguish the product from a naturally occurring one,



- Do not be fooled by the tree that hides the forest:
 - An element, alone, isolated, might not be an unambiguous signature (but an edge fragment or a rearrangement internal to an insert is sufficient for GMOs of transgenesis ...), this is what you are generally asked to consider for NBT (to make you admit that the modification is natural), not all...
 - Various elements collected (see above for NBT and mutagenesis *in vitro* vs. *in vivo*) make it possible to determine the technique employed and then to trace the product by using only a part of the elements (cost aspect, speed... according to the needs of the analysts)
 - These matrix approach practices are already in use (detection of known and unknown GMOs, to reduce costs, simplify complex samples detection ...) and made more user-friendly using the labs' databases and DSS ...

Detection Methods

Available methods

- Phenotypic (ex: tolerance to a herbicide, immunology ...)
- Omics (metabolomic modification, proteomics ...)
- Molecular: genomes and epigenomes / epitranscriptomes (DNA, proteins, RNA):
 - DNA, RNA and modified or unmodified proteins
 - Simplex (PCR, LCR, OLA ...) multiplex (SNPLex, DNA chips ...),
 - From the nucleotide (LCR, OLA ...) to the large chromosomal rearrangement (border fragment ...),
 - Isothermal or not (LAMP, NASBA ...)
 - Combined or not (eg SNPLex = LCR + PCR + DNA chip)
 - Sequencing (Sanger, NGS, ChiSeq, RNASeq ...) with or without reference genome,
 - On isolated tissues or cells, nucleus or organelles,
 - In the laboratory or in the field (PCR, LAMP, sequencing ...)
- Using molecular scars and signatures
 - Univocal (s) or multiple (databases and DSS, see ENGL network works and FP6 Co-Extra program)
 - Analyzes with various software (assemblies, comparisons, phylogeny, statistics, cartographies)
 - Combinable and modular according to the needs: legal identification vs. routine detection



Messages to take home

- There are no technical bottlenecks to distinguish:
 - *In vitro* from *in vivo* mutated organisms,
 - Identify NBT used for producing any product,
 - Detect the derived product
 - Only political and lobbying pressures impeded since 2013 the development of the identification / detection methods of NBT and derived products,
- Worldwide traceability and labeling of NBT products is a inexpensive tool depending only on the wishes of consumers and willingness of retailers

How language matters to get citizens' consent

- The direct impact of using words and expressions on the reasoning and acceptance of both scientists and laypersons (e.g. “*new breeding techniques*”),
- Outrageously simplified language and metaphors (e.g. genome editing) to build up a politically correct language and change the perceptions, thinking and furthermore acting,
- Antiphons using ‘nature’, ‘natural’, ‘traditional’... to facilitate the acceptance of the techniques...

« Mal nommer un objet, c'est participer au malheur de ce monde... »

(Albert Camus, 1944, Poésie 44)



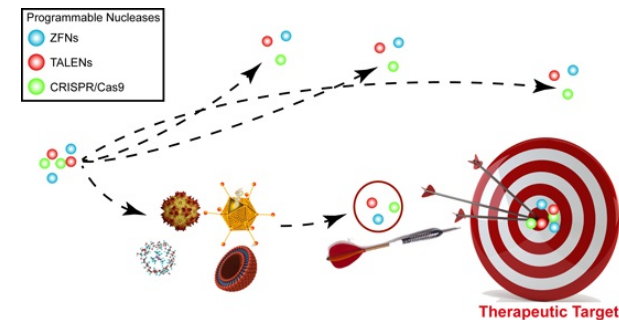
What are precision, unintended modifications and publication's bias?

First training...

Then start ... for missing a lot ...

- Many total or partial homologies in the rest of the genome,
- Thermodynamic considerations,
- Many recipes attempting to reduce the number of off-targets (of a **1,500 factor...**)

- As a result: occasional insertions / deletions or not, chromosomal rearrangements (inversions, translocations...), exon skipping effects, epimutations... difficult to predict and detect...
- Additionnally: false positive not checked, circular reasoning accepted...



Finally, only presumed successful data are published: the usual **bias of publication**

“People just don't have the time to characterize some of the very basic parameters of the system,” says Bo Huang, a biophysicist at the University of California, San Francisco. **“There is a mentality that as long as it works, we don't have to understand how or why it works.”**

Some misleading metaphores

(which influence your perception and then your ways of thinking and finally of acting)

SDN: do not foresee an unique and precise cutting



But a series of cuttings (with numerous breaks to rapidly and accurately stick)



Editing the genome ... Waiting for amending electronic and known languages?



What you have effectively to "edit": untranslated handwritten languages...



plus

The promised precise modification?



Several 'off targets' obtained due to rebound effects from homologous sequences



It's rather Staline's organ shots

Targeted mutagenesis: were you thinking about a 'one shot'?



On a destructed landscape due to related techniques: everything to rebuild



Links of interest

- Direct:
 - e.g. scientist paid by a stakeholder, published results are generally more favorable to the funding companies...
 - Your company or public research institute and its policies, hierarchy and carrier...
- Indirect: institutional... e.g. lab. funding and temporary positions of team's personnel (e.g. backlash from colleagues in position to influence the results of your research proposals),

Message to take home: you cannot expect a scientist selling the entire week a technique such as NBT, for funding his/her team, to change his/her state of mind and being critical when entering into an expertise's room...

Bioethics

- Enhanced gene drive: organisms' eradication (despite it is already known it is unsustainable) means a privatization of public health policies (see. WHO director's statements at the appearance of Zika, Chikungunya... viruses in Brazil...)
- Plants as a proof of concept, to test the accuracy of the methods,
- Huge demand of perfect children, particularly in some countries...

As for GMOs, large differences observed in polls in western countries about changes of human somatic vs. germinal lines, as well as for pharmaceuticals issued from modified organisms (different 'cost-benefits' analyses).

Recurrent politician interferences

- The abuse of metaphors and other rhetoric effects, oversimplified statements, the confusion between science and applications / innovations,
- Choice of experts and of the committees' chairs, creation of appropriate new structures when political decisions have not been endorsed by the current expertise areas (e.g. European SAM with "high level" experts),
- Requests of changes in e.g. the coexistence issues of GM and non-GM fields production: isolation distances with negotiations between farmers vs. territory management, measurement units to be changed (ENGL advice requested...),
- French OPECST's chair, claiming '*we have to avoid with Crispr-Cas9 the current situation of GMOs' refusal by European citizens*' (online video, report),
- European commissioner declaring in January 2018 it would prefer NBT product being not traceable (ENGL proposed in 2013 to the EC to develop the identification methods)...

How to improve expertise?

- Recognizing early societal issues, developing the democracy of techniques by e.g. citizens' consensus conferences to establish guidelines (on e.g. expertise, NBT...),
- Training of experts to professional ethics, compliance with rules, future scientists to philosophy, history of science, professional ethics, controversy and dissent...
- Favoring the valorization of expertise and critical thinking, developing appropriate expertise tools (e.g. Delphi method),
- Assessing the quality of work of experts to avoid the collections of nominations, establishing independent professional ethics committees in all expertise instances, promoting responsibility and sanctions...

How to deal with expertise's biases such as links of interest?

- Better recognition of the experts' involvement: emoluments, careers' evaluation...
- Better recognition and detection of the *a priori* opinions of the experts in an expertise work,
- Developing and using experts' elicitation tools: Delphi, Q methods (see the current FRB's call for expertise on synthetic biology and environment), involvement of young more critical experts protected from backlash...
- Improving the weight of evidence? Scientific collective expertise according to recognized quality standards and rules (see e.g. Inra's EsCo), systematic literature reviews, meta-analyses... But how could the democratic debate be maintained (NGOS expertise in front of e.g. a SLR)?

Messages to take home:

- links of interest cannot be fully discarded, we have to find combined ways to 'manage' them and control the success of the procedures, and the quality of experts' work,
- Citizens' conferences should be launched to allow people to discuss about the corresponding choices of society and to establish guidelines as in 1998 on GMOs,
- Stakeholders' fora, such as the HCB's CEES on socio-economics issues, should be favored.

After decades of expertise, such as for the HCB, i like to remind this sentence of
Pierre Gilles de Gennes (Nobel laureate) :

*« You know, experts are often like the military.
They are experts of the last war but not of the next... »*

Thank you for your
attention

