JOHNS HOPKINS
BLOOMBERG SCHOOL
of PUBLIC HEALTH

New Approaches to Tox Testing

Slides available

Thomas Hartung & team

frontiers in Artificial Intelligence

Field Chief Editor

frontiers in Big Data

AstraZeneca

ATCC

AxoSim
Human Data, Faster.
VP, shareholder

MPS

insphero

Apellis

Pyrogen

MERCK MILLIPORE

BIOMÉRIEUX

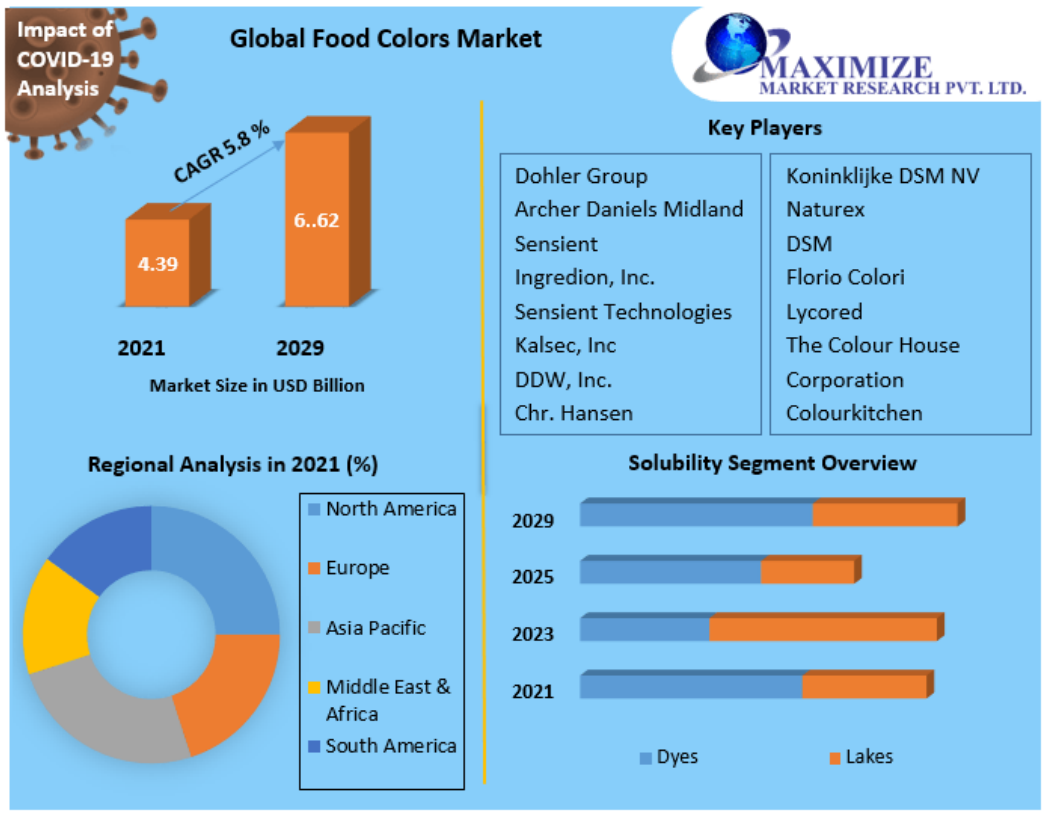
A.I.

UL **Consultant**

Green Chemistry Advisory Panel

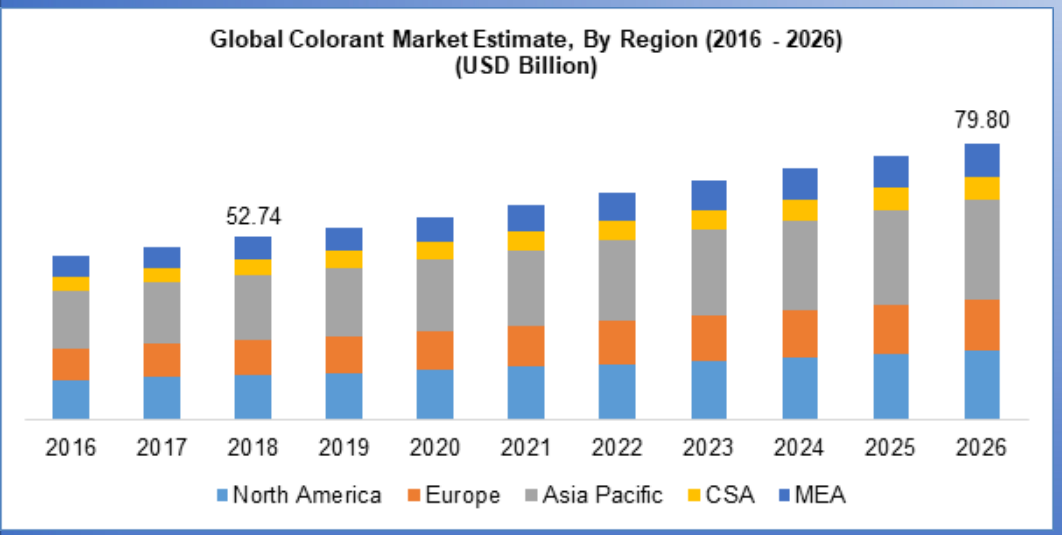
ToxTrack
Consultant, shareholder

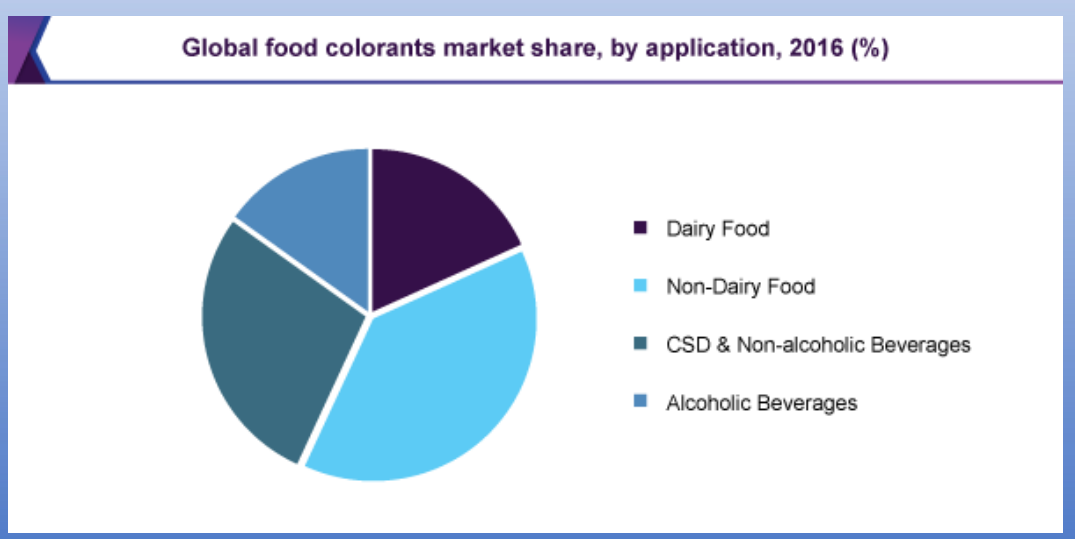
In preparation: Insilica LLC



Food colors

- An expanding industry
- Supporting many industries
- Relatively limited numbers of substances
- Synthetic and natural





Complex regulatory requirements

CODEX
International Food Standards
ALIMENTARIUS

World Health Organization

FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS

Supported by

HACCP
Hazard·Analysis
Critical·Control·Point

efsa
European Food Safety Authority

Food Quality System

https://gd-innovations.com/our-product-category/digital-supply-chain/

About 400 accepted and tightly controlled food additives in Europe

http://thearticlebay.com/en-gb/article/109-overall-information-on-food-additives

Those permitted before 20 January 2009 are going through a new risk assessment by EFSA by the end of 2020.

E102-143 = artificial colors

https://foodlawlatest.com/2015/03/30/guidance-document-describing-the-food-categories-of-regulation-ec-no-13332008-on-food-additives/

Karmaus et al. (2016)

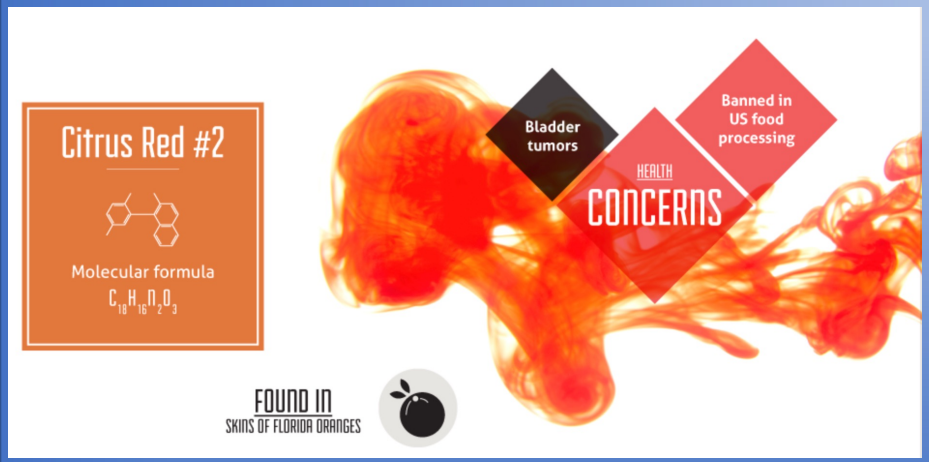
8,659 food-relevant chemicals

- **3,888 direct additives**
- **4,771 were food contact substances or pesticides**

Neltner et al. (2013a)

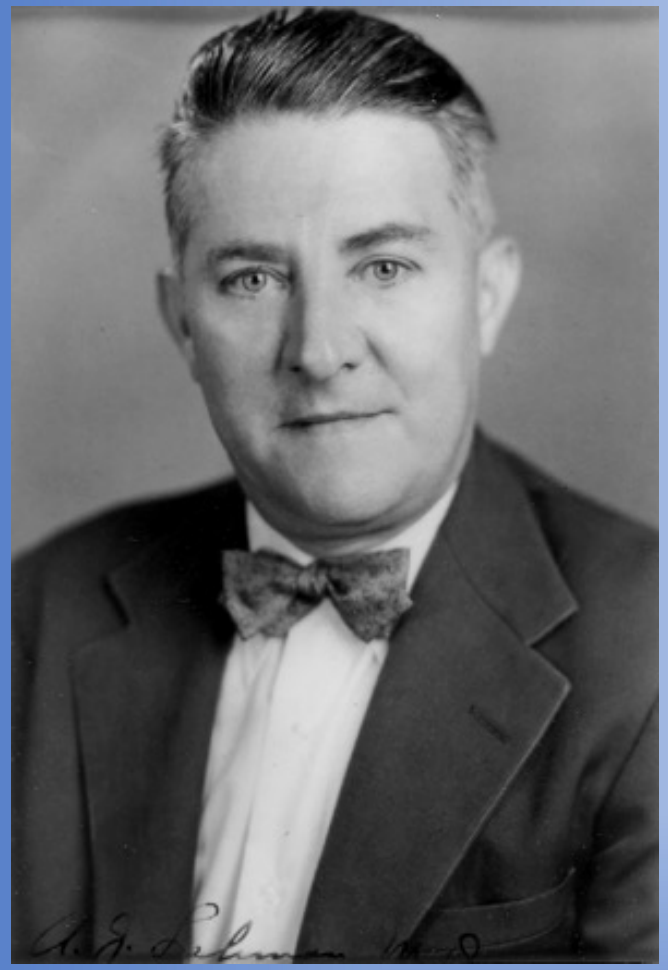
- **Less than 38% of FDA-regulated additives have a published feeding study**
- **21.6% direct additives have feeding studies necessary to estimate a safe level of exposure and 6.7% have reproductive or developmental toxicity data in FDA's database**

Public concerns whether justified or not



Cancer
ADHD / autism
Asthma

https://www.special-education-degree.net/food-dyes/



"You too can be a toxicologist in two easy lessons, each of ten years."

Arnold F. Lehman, FDA

Traditional Toxicology

- Find lowest dose with effect
- Divide by 100

= safe for humans

It usually works,
but if we had 12 fingers,
we would be 44% more safe…

Toxicology

$4 billion per year *in vivo*

$20 million per pesticide
$5m for REACH HPV chemical

$1 million for a cancer study

About 5 years

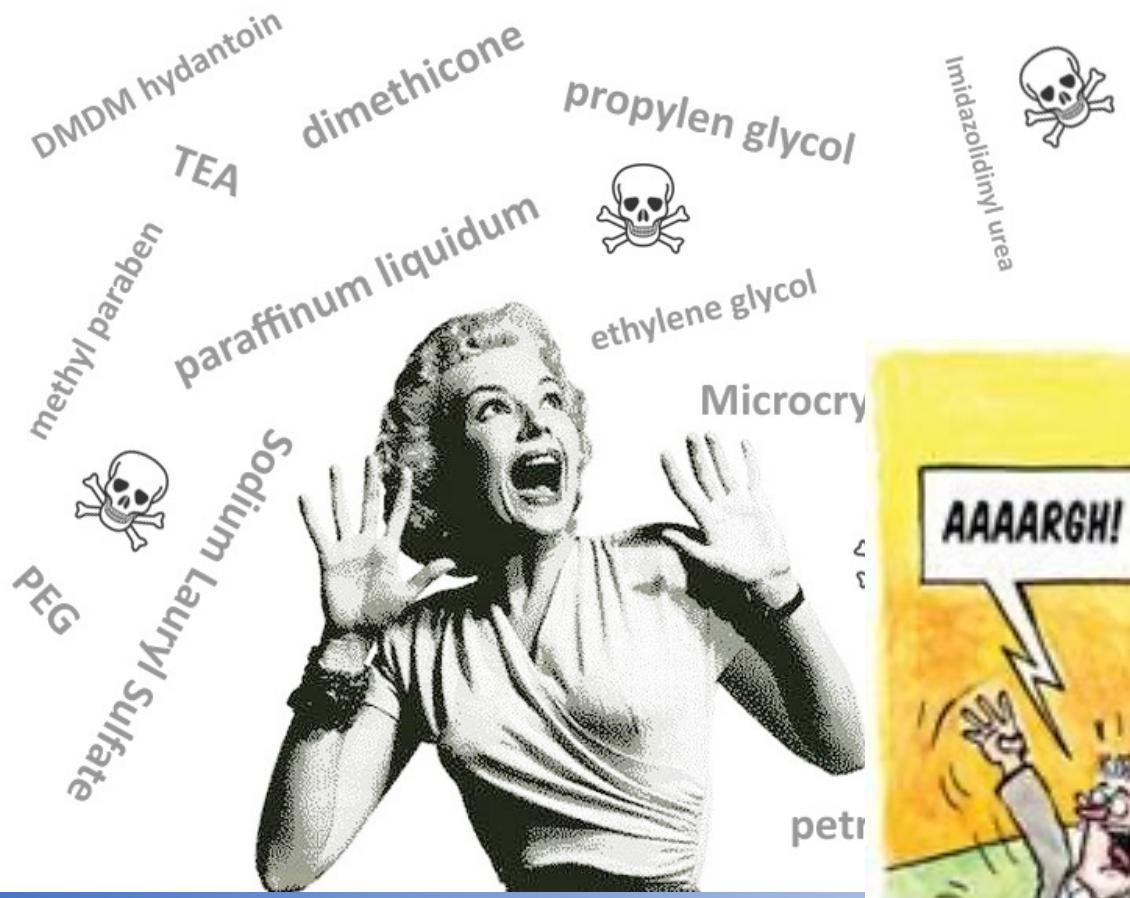
20kg needed

It is easy to scare with the presence of chemicals

TELL SPRECHER BREWING CO:

TOXIC CHEMICALS DON'T BELONG IN OUR BEVERAGES!

Toxic-Free FOOD



Chemophobia

Rollini et al., Chemophobia: A systematic review
Tetrahedron 113, 2022, 132758

Philippus Aureolus Theophrastus Bombastus von Hohenheim, also known as Paracelsus

“The father of toxicology” ~500years ago

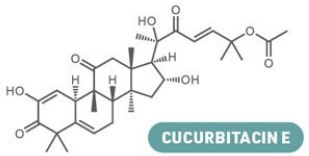
THE DOSE MAKES THE POISON

Synthetic chemicals are not more toxic than natural ones

TOXINS IN FRUITS AND VEGETABLES

People often worry about the safety of chemicals added to their food. But sometimes, nature itself can produce harmful compounds in the foods we eat. Here we look at a selection of toxins found in common fruits and vegetables.

GOURDS



CUCURBITACIN E

Pumpkins and other gourds and squashes produce cucurbitacins to deter insects. In rare cases, cross-pollination or inadequate growing conditions result in elevated levels of cucurbitacin E. This compound leads to a bitter taste and can cause toxic squash syndrome, which includes nausea, vomiting, and diarrhea.

KIDNEY BEANS

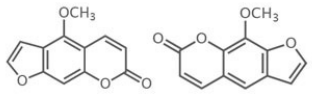
HEMAGGLUTINATION UNITS[a]

70,000 UNCOOKED | 200–400 COOKED

a Measure of phytohemagglutinin content in one kidney bean.

Kidney beans contain phytohemagglutinin, a plant protein that in high amounts causes nausea, vomiting, and diarrhea. As few as five raw beans can be enough to cause sickness. Thorough cooking is required to reduce the quantity of phytohemagglutinin in the beans to safe levels.

PARSNIPS

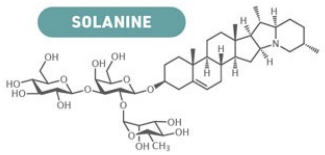


BERGAPTEN XANTHOTOXIN

Parsnips and celery contain furanocoumarins, such as bergapten and xanthotoxin, to defend against organisms that might eat the plants. The higher levels of furanocoumarins in the vegetables' shoots and leaves can cause phytophotodermatitis, which makes the skin sensitive to sunlight, when people handle the vegetables.

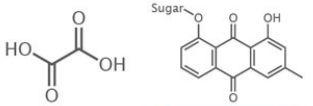
POTATOES

SOLANINE



Potatoes produce solanine as a defense against insects. It's harmless to people at the levels normally found in potatoes. However, when potatoes are exposed to light, they turn green and produce solanine at potentially harmful levels. Solanine poisoning can cause vomiting and diarrhea.

RHUBARB



OXALIC ACID ANTHRAQUINONE GLYCOSIDES

Eating rhubarb leaves can result in nausea and vomiting because of the high levels of oxalic acid. Some scientists think that other poisonous compounds in the leaves, such as anthraquinone glycosides, may contribute to the leaves' toxicity. The stalks are safe to eat because they contain lower oxalic acid levels.

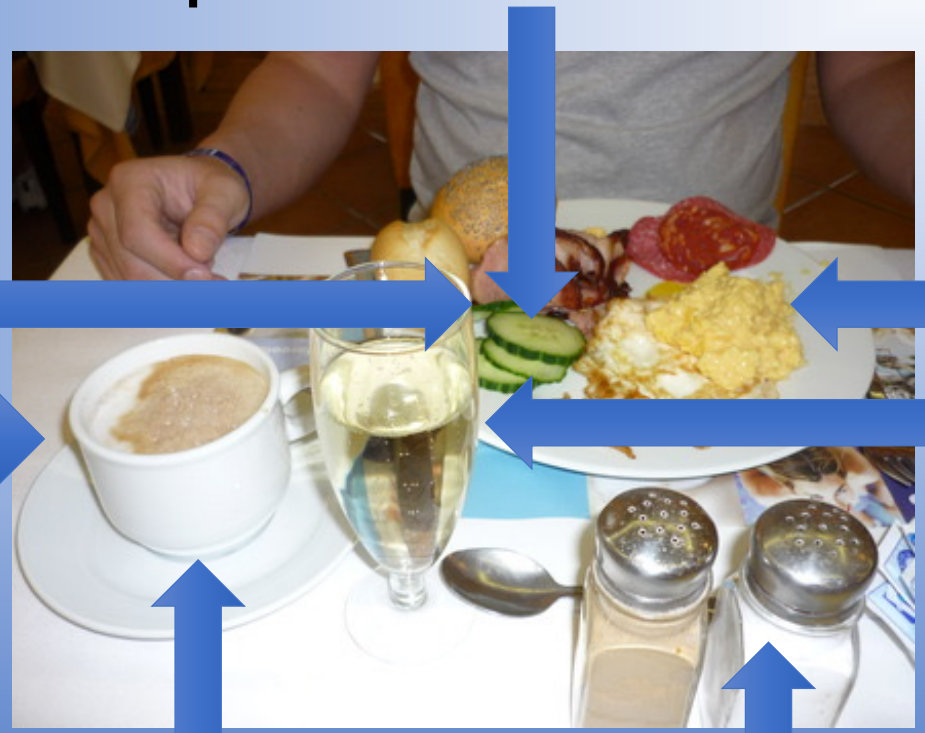
PERIODIC GRAPHICS

A plant extract can have thousands of substances

Some toxicology challenges for food

Protected against minute amounts of pesticides

Natural pesticides 10,000x more, 35 of 63 carcinogenic



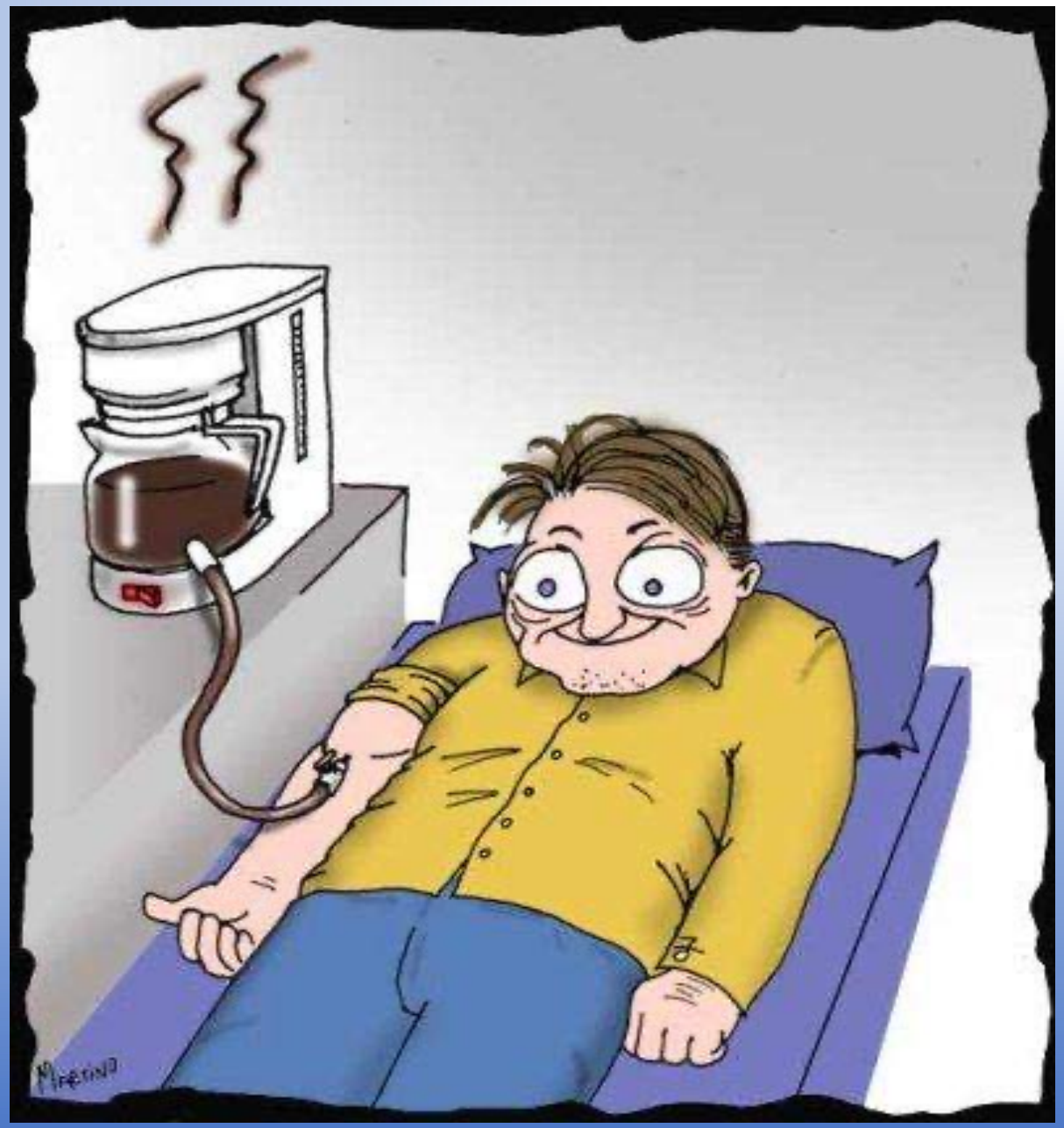
Protected against dioxin in eggs

23 of 32 tested coffee ingredients carcinogenic

Same calculation for alcohol: One glass per 345 years

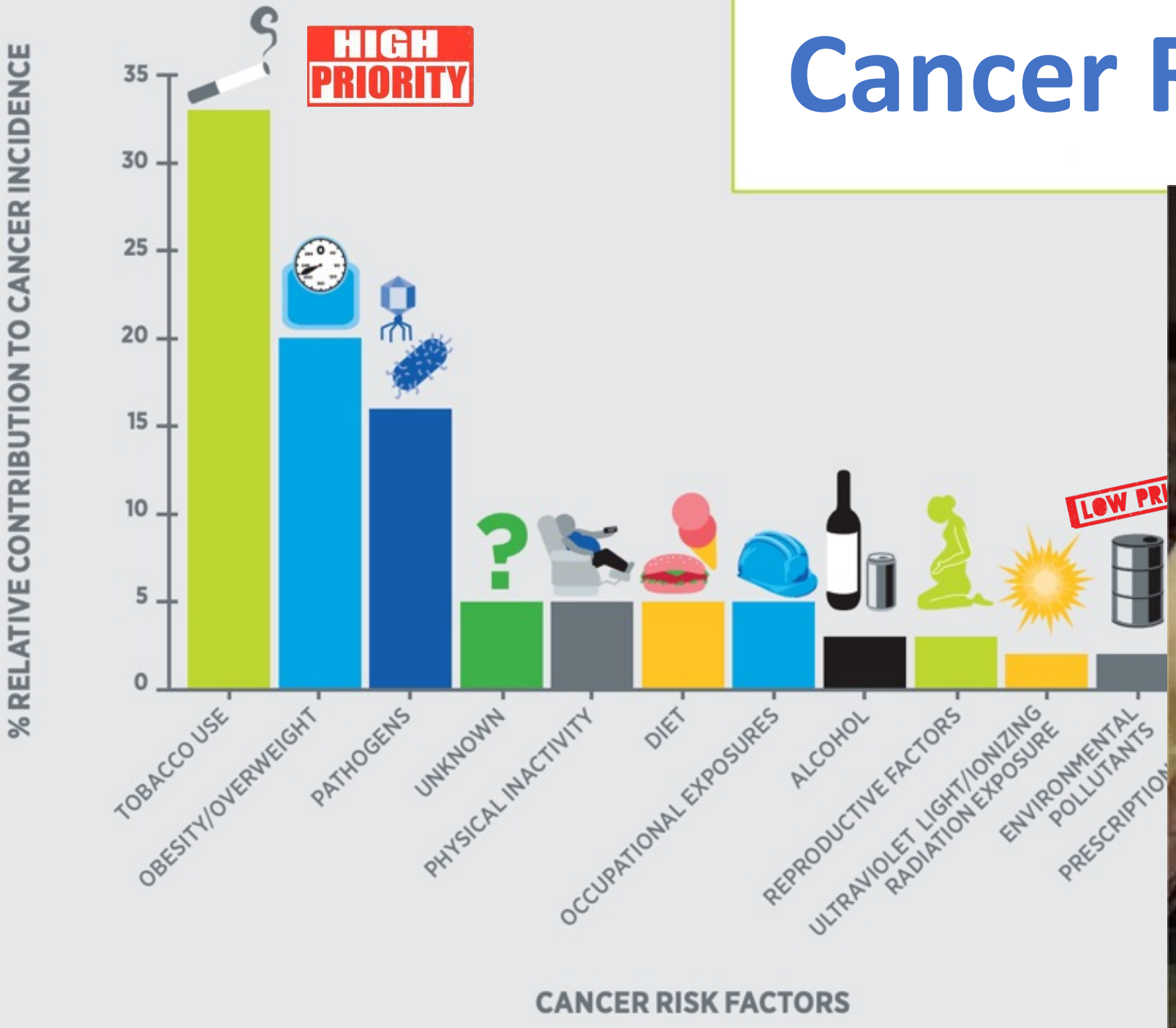
Genotoxic: sugar

Genotoxic: salt



Despite various carcinogens, coffee drinking is actually reducing liver cancer

Cancer Risk Factors



Coke had to change recipe after 140 years

Caramel dye carcinogenic in rats at dose eqivalent to 8,500 tins per day bacause of Delaney clause

Cancer animal tests are:

- **57% repro-ducible (n=121)**
- **57% concordant between rat and mice**
- **Increase from 50 to 200 animals would lead to 92% pos. chemicals**

Broad cancer testing would be a disaster!

Probably few carcinogens, but especially in the US too few checked!

Problem: Comprehensive assessment $5-20 million per substance

Concern – use of food additives for vaping

Colored Vape Smoke as an Art Form – It's Fascinating!

You Can Add Coloring Agents to Any Vaping Mod

If you want to get those vibrant colors, you'll have to add the agent to the vaping mod before loading the e-liquid. You can use any food additives to get those brilliant hues. Let's walk you through the steps of how to make that happen.

- **2014: 7,700 flavors (+200/month)**
- **75% contain diacyl, known to produce "popcorn lung"**
- **85% sold through web mainly out of China**

https://blackoutvapors.com/colored-vape-smoke-as-an-art-form-its-fascinating/

S1B(R1) Addendum to S1B Testing for Carcinogenicity of Pharmaceuticals

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

November 2022
ICH

"Application of this integrative approach reduces the use of animals in accordance with the 3R (reduce/refine/replace) principles and shifts resources to focus on generating more scientific mechanism-based carcinogenicity assessments, while continuing to promote safe and ethical development of new pharmaceuticals."

Toward the end of the cancer bioassay

EU: Some enforcement is coming

View online

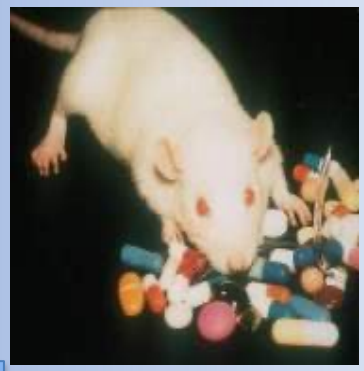
ECHA Weekly

Next EU-wide REACH enforcement project to focus on imported products

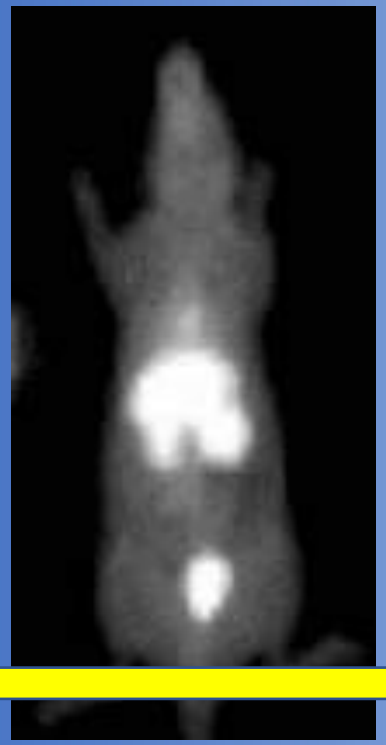
The next REACH enforcement project will investigate how companies fulfil the registration, authorisation and restriction obligations for products and chemicals they import from outside the EU.

The project will be done in 2023-2025 and will require close cooperation between REACH enforcement and national customs authorities in the Member States.

Interspecies prediction of cancer



Concordance 57%



Animal test Cancer

18-24 months

$1 million

4-600 animals

53% positive

Estimate human 5-20% positive

29 trichloroethylene carcinogen risk assessments

4x “carcinogen”

19x “equivocal”

6x “non-carcinogen”

Rudén C. *Regul. Toxicol Pharmacol 2001; 34: 3-16.*

Testing multiple statistical hypotheses resulted in spurious associations: a study of astrological signs and health

PC Austin et al., J. Clin. Epid. 59, 964-969, 2006

Study:

All 10,674,945 residents of Ontario (18-100 years) in 2000.

Randomly assigned to equally sized derivation and validation cohorts and classified according to their astrological sign.

Derivation cohort searched for 223 of the most common diagnoses.

Results:

24 associations tested in validation cohort:

Leo ➔ gastrointestinal hemorrhage (P=0.0447)

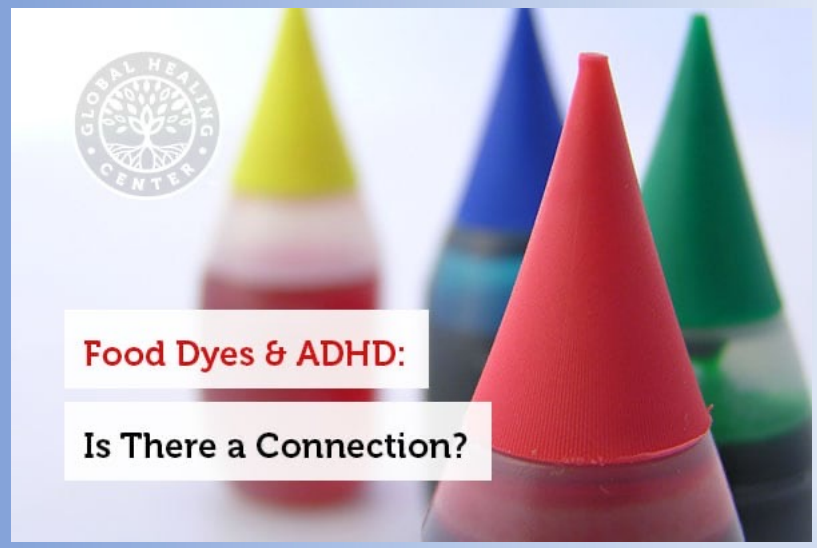
Sagittarians ➔ humerus fracture (P=0.0123)

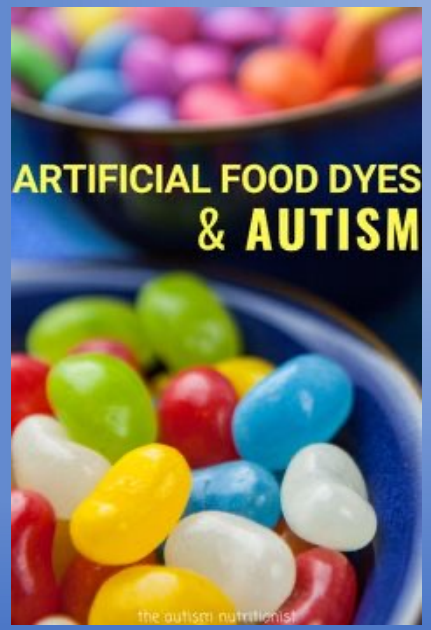
Conclusions: Testing of multiple, non-prespecified hypotheses increases the likelihood of detecting implausible associations.

In toxicology: 28d study ➔ 40 endpoints, cancer bioassay ➔ 60 endpoints

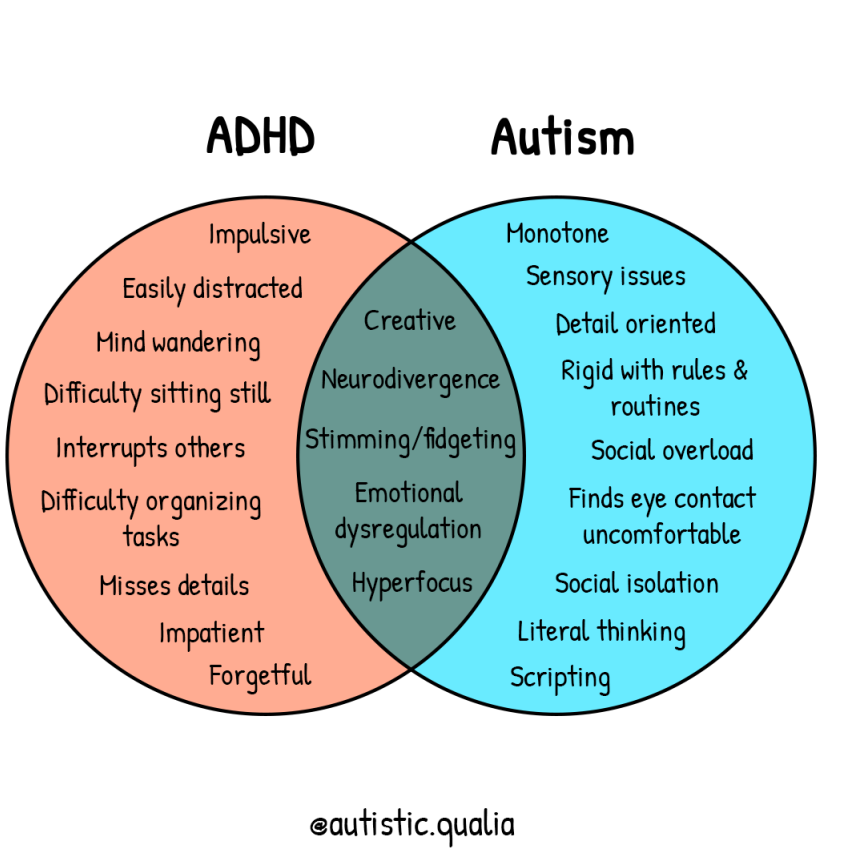
two-generation study ➔ 80 endpoints


3 THINGS YOU MUST KNOW ABOUT
AUTISM & FOOD DYE
the autism nutritionist


GLOBAL HEALING CENTER
Food Dyes & ADHD:
Is There a Connection?

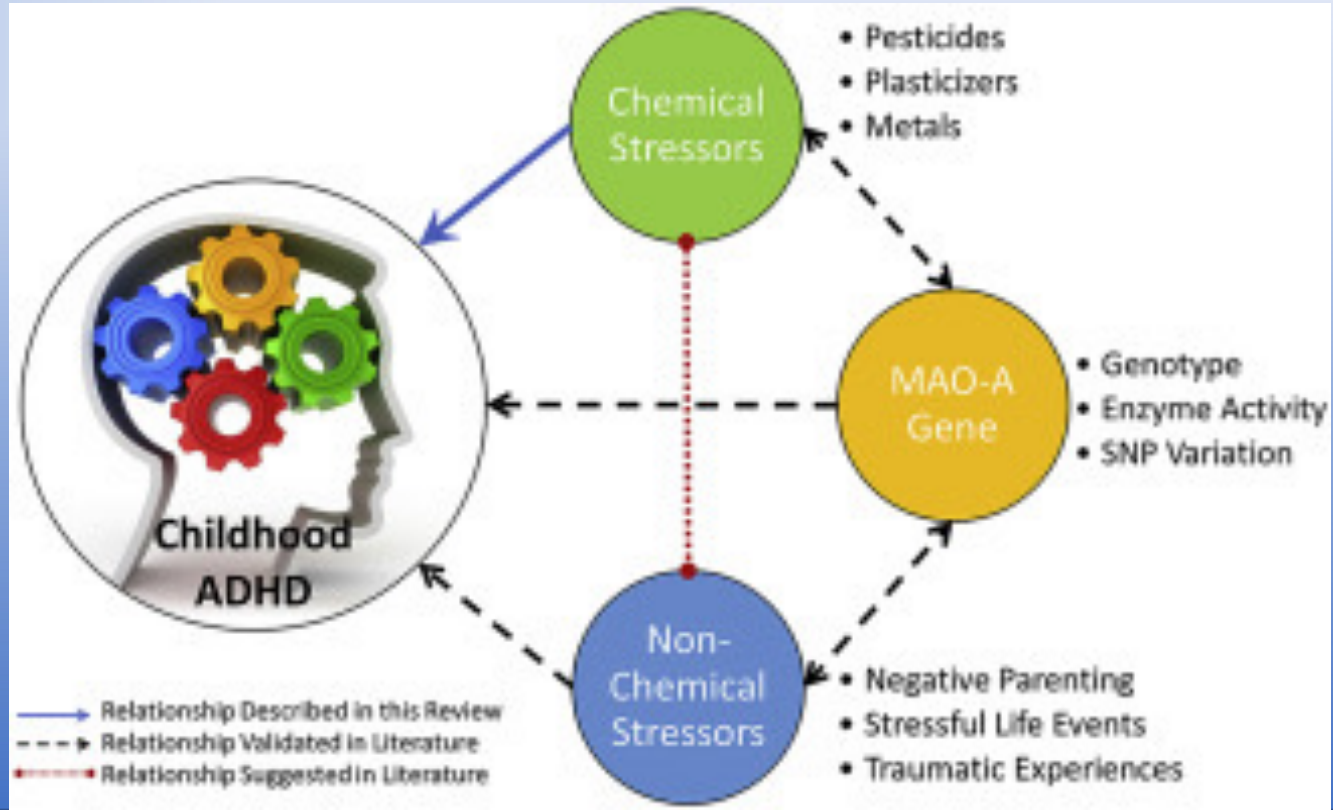

ARTIFICIAL FOOD DYES
& AUTISM
the autism nutritionist


ADHD STILL Linked to Food Dyes!
Of the 3 most commonly used synthetic dyes in the US,
Tartrazine
Allura red
Sunset Yellow
The #1 KNOWN HEALTH EFFECT is:
Hyperactivity
Because of this health concern,
these FOOD DYES are BANNED in Europe.
The US won't even allow a warning lable!

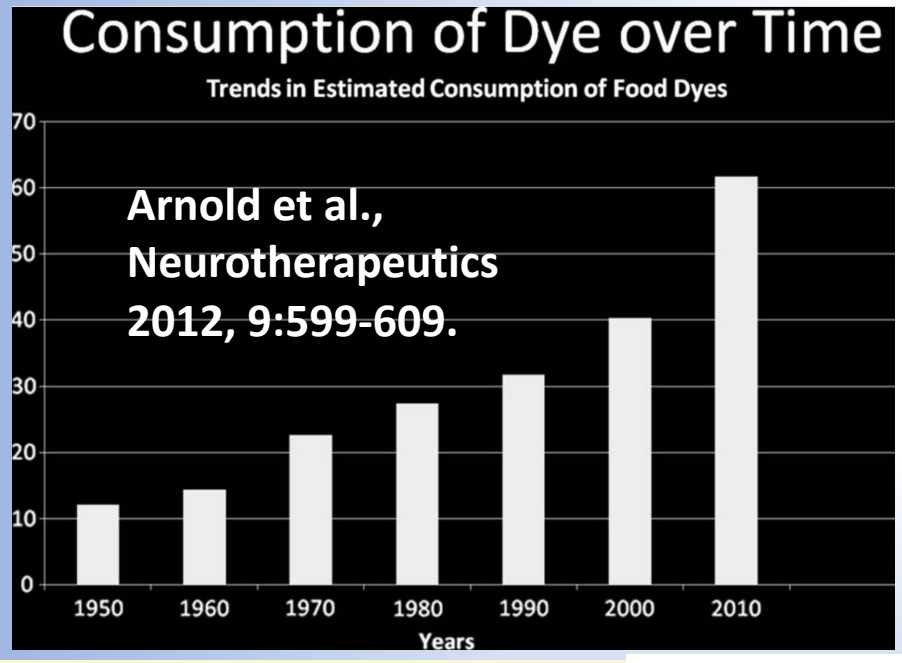


Autism & ADHD

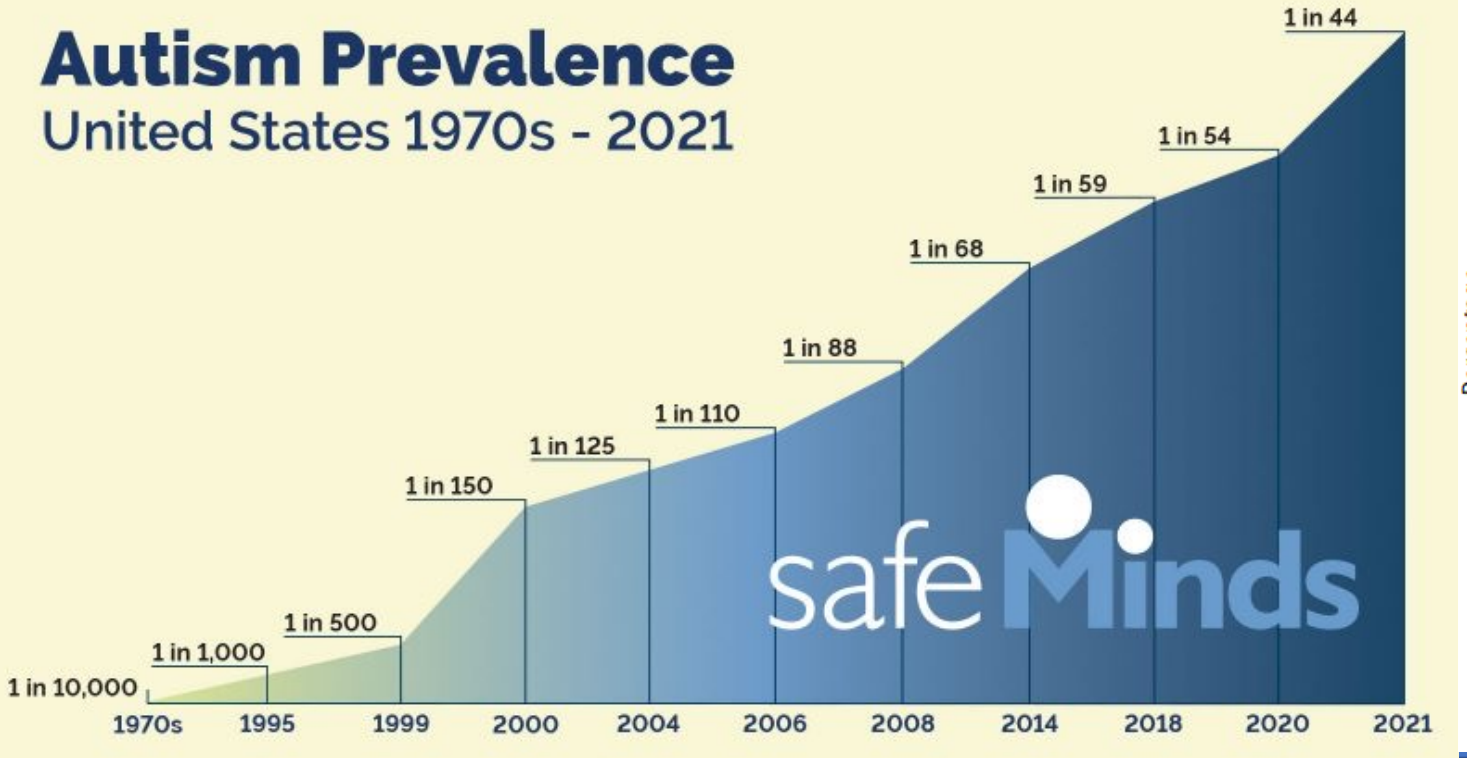
- Developmental neurological problems
- Rising incidence
- Similar chemicals suspected

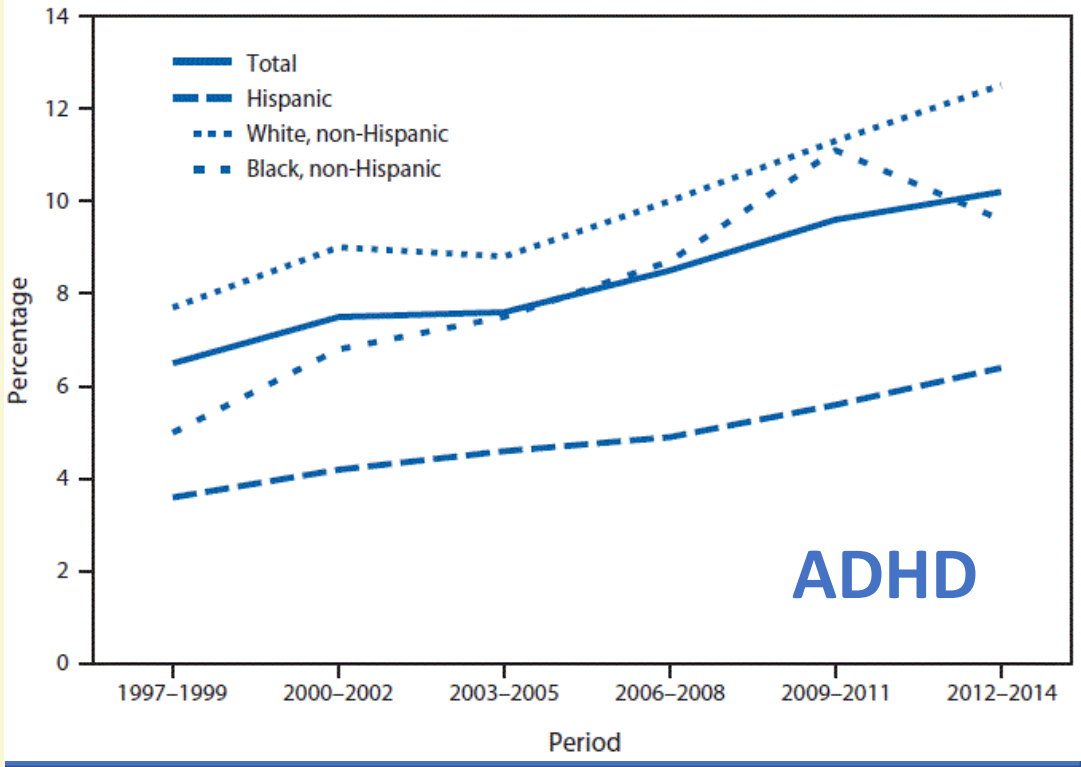



AUTISM


Consumption of Dye over Time
Trends in Estimated Consumption of Food Dyes
Arnold et al.,
Neurotherapeutics
2012, 9:599-609.
70
60
50
40
30
20
10
0
1950
1960
1970
1980
1990
2000
2010
Years

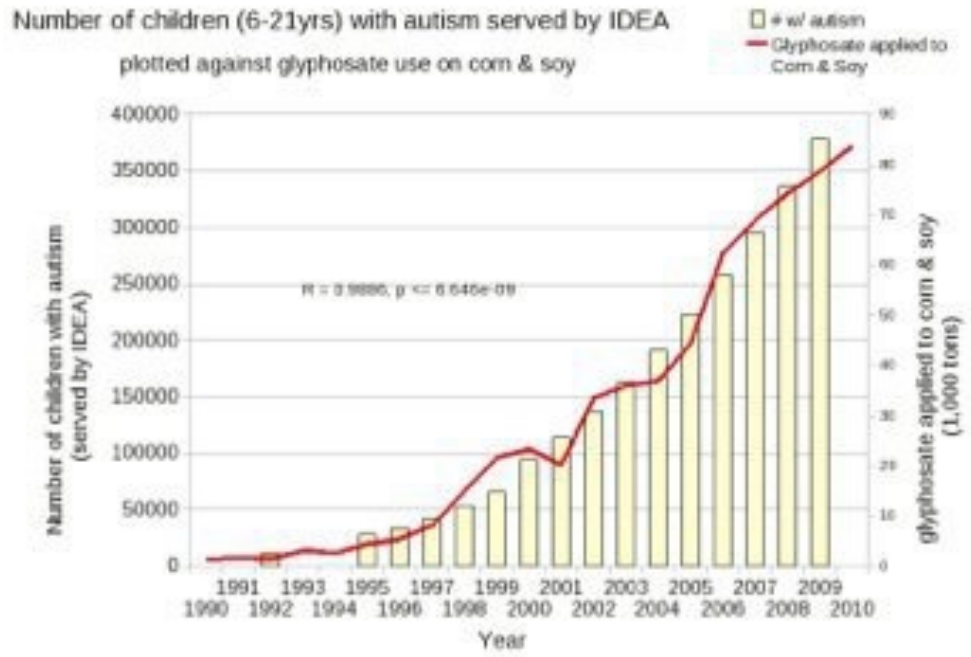

ADHD


Autism Prevalence
United States 1970s - 2021
1 in 10,000
1 in 1,000
1 in 500
1 in 150
1 in 125
1 in 110
1 in 88
1 in 68
1 in 59
1 in 54
1 in 44
1970s
1995
1999
2000
2004
2006
2008
2014
2018
2020
2021
safeMinds


Total
Hispanic
White, non-Hispanic
Black, non-Hispanic
Percentage
14
12
10
8
6
4
2
0
1997–1999
2000–2002
2003–2005
2006–2008
2009–2011
2012–2014
Period
ADHD

The mistake of correlation ≠ causation is repeated in science and society again and again…

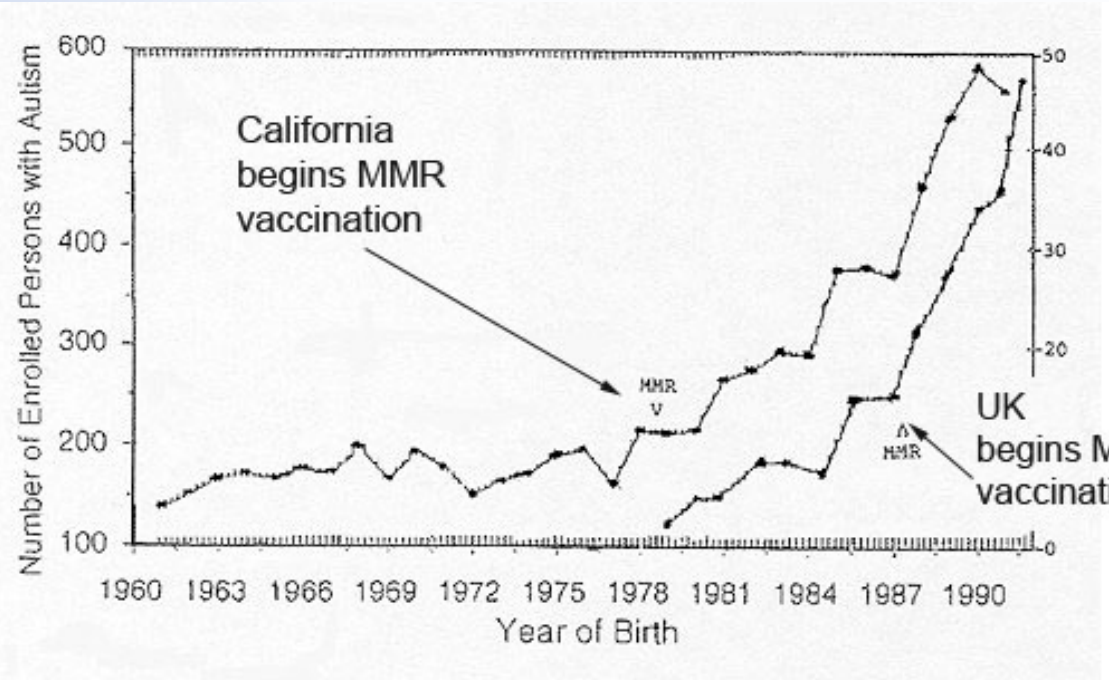
Glyphosate and Autism*



Pearson Correlation Coefficient = 0.99

*Nancy Swanson, http://www.examiner.com/article/data-show-correlations-between-increase-neurological-diseases-and-gmos

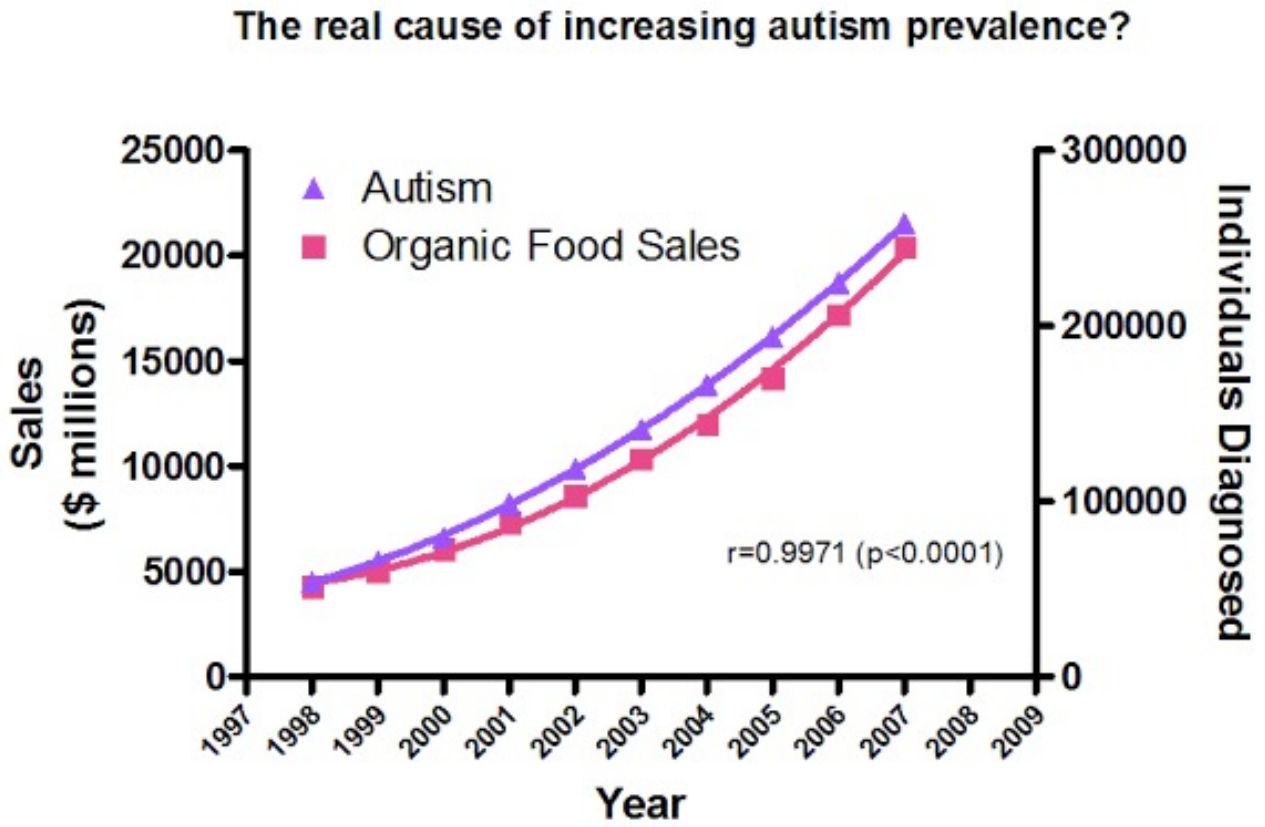
MMR vaccination and autism

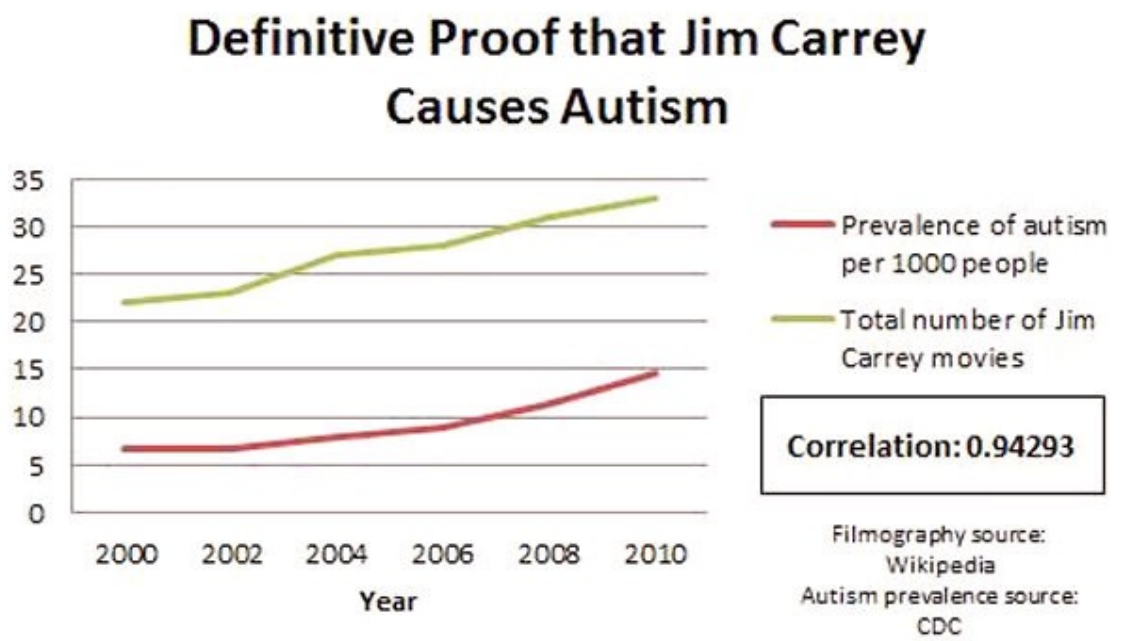


http://spnh.com.au/correlation-causation-and-context-in-the-health-industry/

Wakefield et al. 1999. The Lancet 354:949-950.

We could show many spurious correlations as well….





http://9gag.com/gag/a1YX5rw/the-real-cause-of-autism


Animal test:
$1.4 million
1,400 animals
200 chemicals tested:
No regulatory
consequence

DNT from *in vivo* towards *in vitro*

DNT3 Developmental Neurotoxicity

TestSmart DNT Developmental Neurotoxicity

ISTNET Workshop

efsa OECD

Expert Group on DNT

OECD

Guidance Document

2005 2010 2015 2020

TESTSMART DNT2 DEVELOPMENTAL NEUROTOXICITY

TESTSMART DNT4 DEVELOPMENTAL NEUROTOXICITY

transatlantic think tank for toxicology

Test Readiness

TESTSMART DNT5 DEVELOPMENTAL NEUROTOXICITY

STAR grant

FDA

transatlantic think tank for toxicology

DNT Reference Compounds

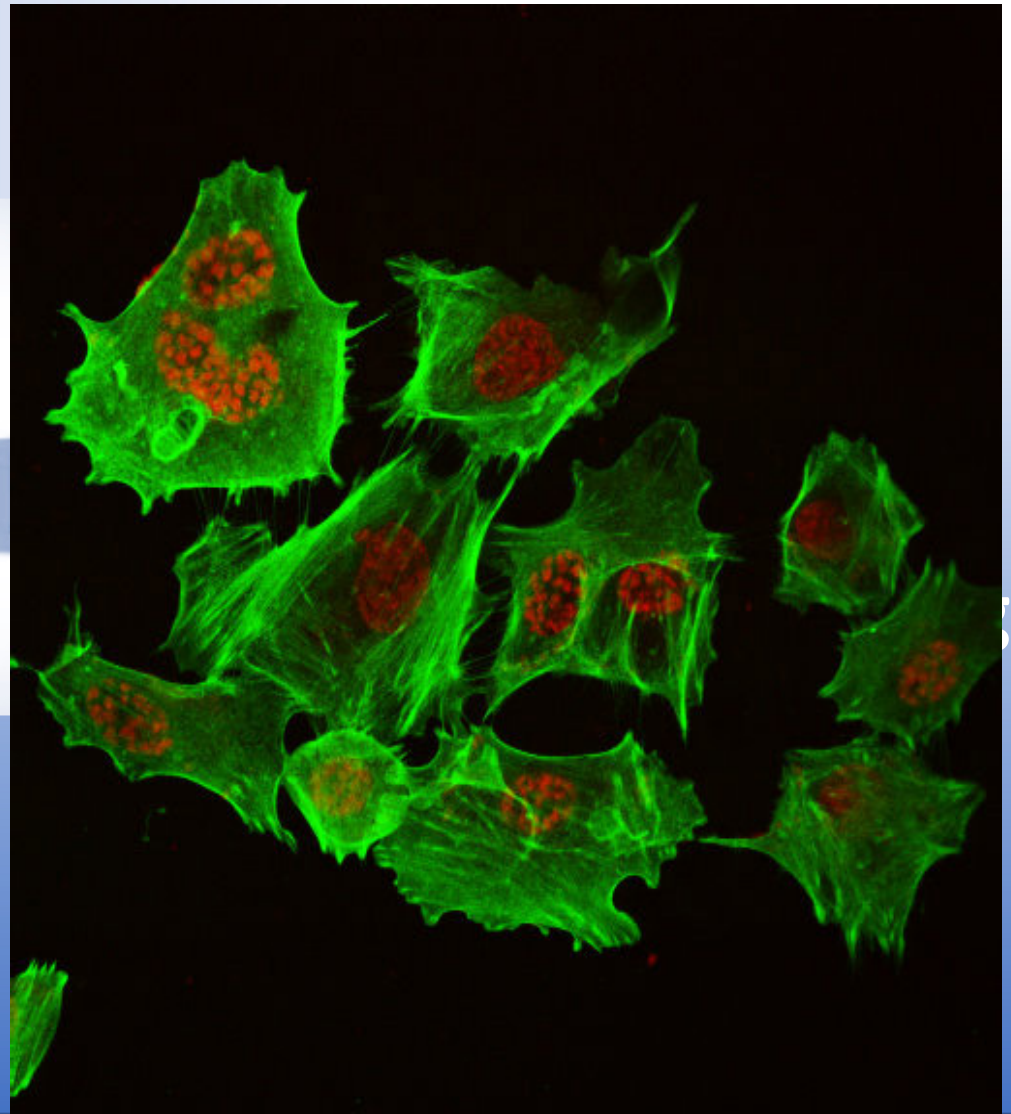
FDA CERSI Johns Hopkins University

Human cell and tissue culture

Irreprodu-*ce*ll-bility

Primary cells of limited access, quality, and quantity

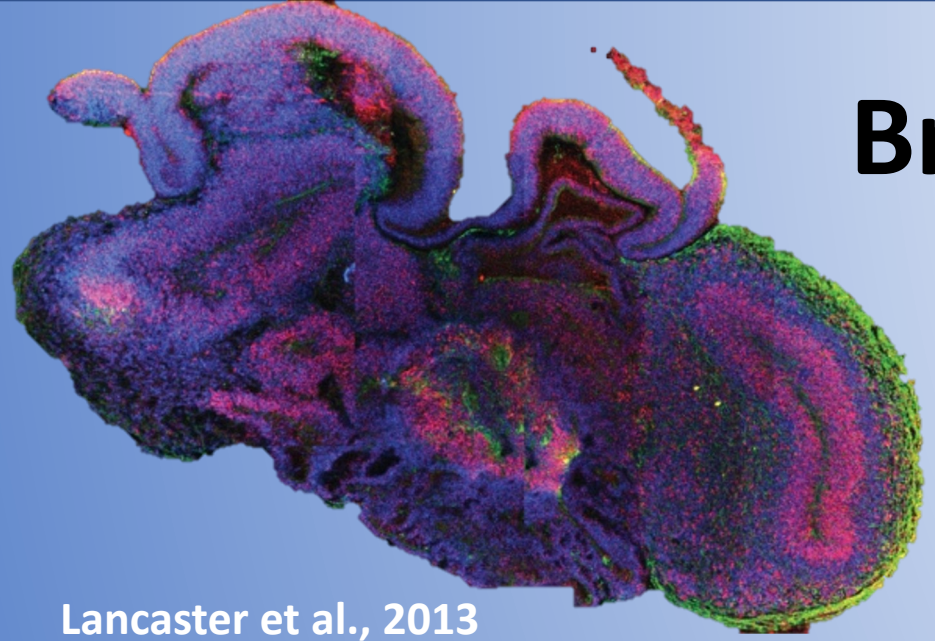
Tumor cell lines



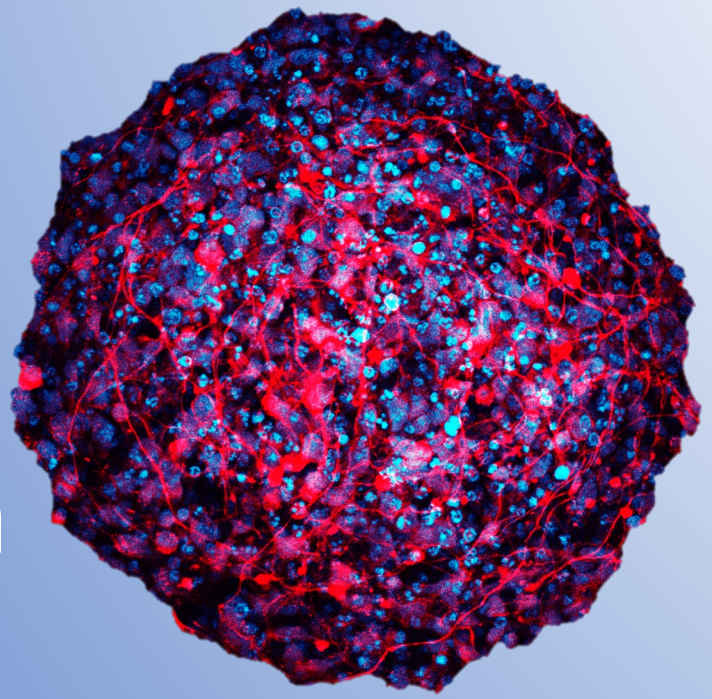
…gical

- **Ca. 25% of cell lines misidentified**
- **15-25% mycoplasma infected**
- **Genetic instability**
- **Culture artifacts**

Brain Organoids



Lancaster et al., 2013



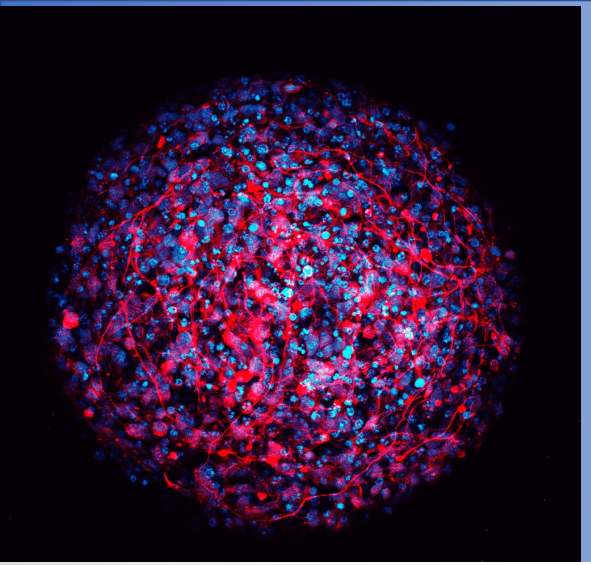
Autism

COVID-19

Glioblastoma

....

2016



DNT in human brain organoids

frontiers **Front Cell Neurosci 2020**

Antidepressant Paroxetine exerts developmental neurotoxicity in an iPSC-derived 3D human brain model

Xiali Zhong[1, 2], Georgina Harris[1], Lena Smirnova[1], Valentin Zufferey[3], Rita Sa[4], Fabiele Baldino Russo[5], Patricia C. Baleeiro Beltrao Braga[5], Megan Chesnut[1], Marie-Gabrielle Zurich[3], Helena Hogberg[1], Thomas Hartung[6, 7], David Pamies[3, 1*]

Tox Appl Pharmacol 2018

Contents lists available at ScienceDirect

Toxicology and Applied Pharmacology

journal homepage: www.elsevier.com/locate/taap

Rotenone exerts developmental neurotoxicity in a human brain spheroid model

David Pamies[a], Katharina Block[a], Pierre Lau[b], Laura Gribaldo[b], Carlos A. Pardo[c], Paula Barreras[c], Lena Smirnova[a], Daphne Wiersma[a], Liang Zhao[a,d], Georgina Harris[a], Thomas Hartung[a,e], Helena T. Hogberg[a,*]

Archives of Toxicology
https://doi.org/10.1007/s00204-020-02903-2

Arch Toxicol 2021

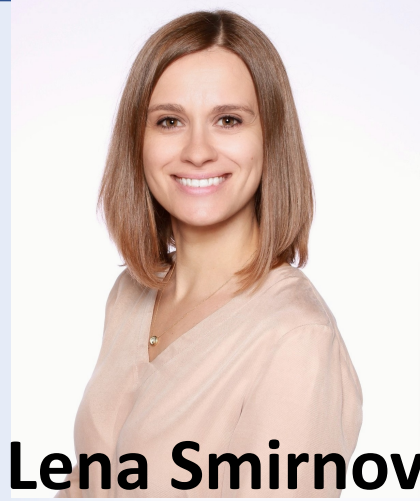
ORGAN TOXICITY AND MECHANISMS

Organophosphorus flame retardants are developmental neurotoxicants in a rat primary brainsphere in vitro model

FDA

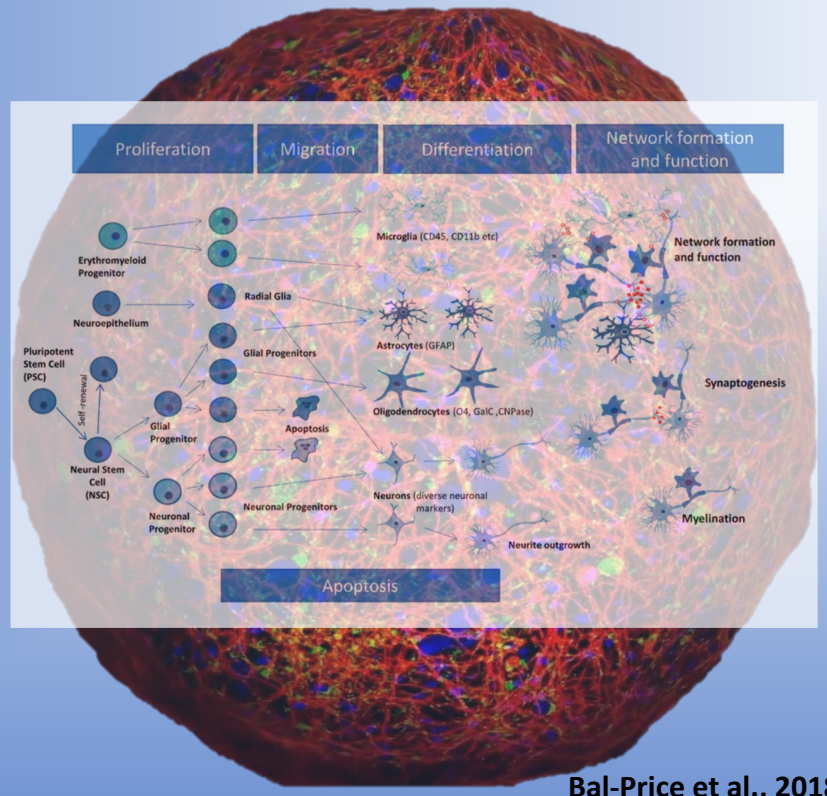
NTP National Toxicology Program
U.S. Department of Health and Human Services

6-in-1 BrainSphere assay to test Neurodevelopment



Lena Smirnova

Neuronal differentiation
Myelination
Neurite outgrowth
Synaptogenesis
Glia migration & Gliosis
Neural network (E-phys)



Bal-Price et al., 2018a

CRISPR/CAS9

Reporter/
Fusion
proteins

Mini- Brainbow

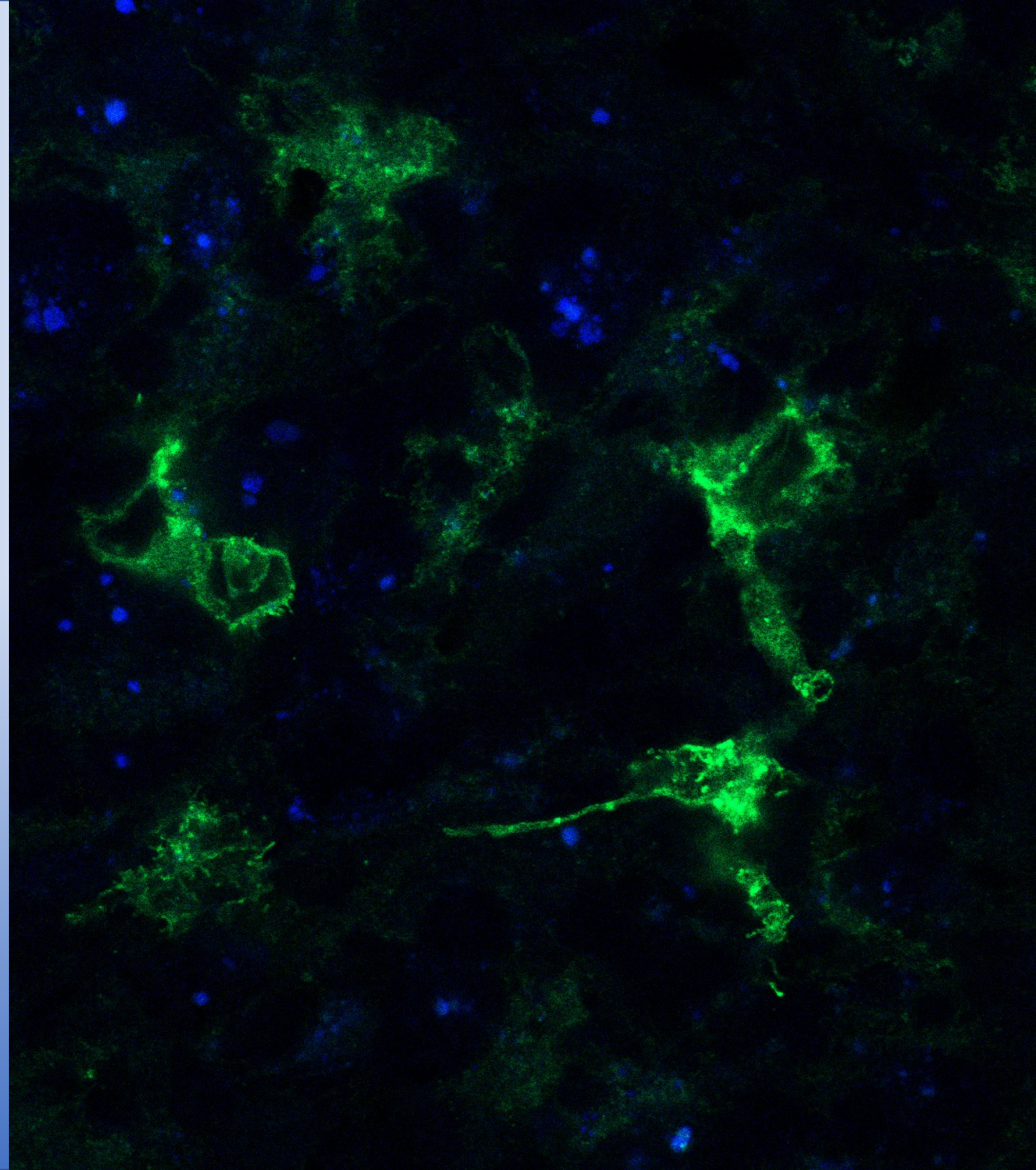
Neurons
Astrocytes
Oligodendrocytes
Synapses
3D electrophys

High content imaging
Toxicant/drug screening

CRISPR/Cas9 Knock-Ins

Oligodendrocytes (PLP-GFP)

Synapsis (Synaptophysin-BFP)

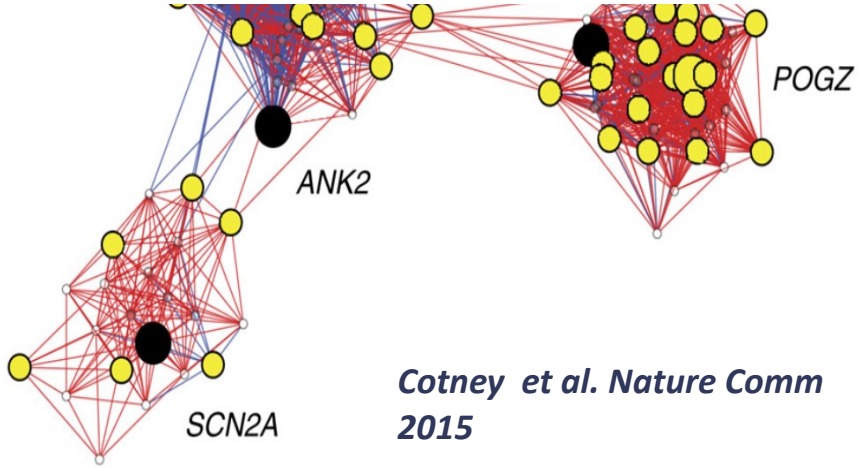


Bloomberg School Researchers Awarded $11.7 Million Five-Year NIH Grant to Build and Lead Autism Center of Excellence Network

Published **September 08, 2022**

DISABILITY

Network will aggregate global research projects studying gene-environment interaction to understand autism's causes and to improve quality of life among autistic individuals



Cotney et al. Nature Comm 2015

Functional and Molecular signatures

Lena Smirnova

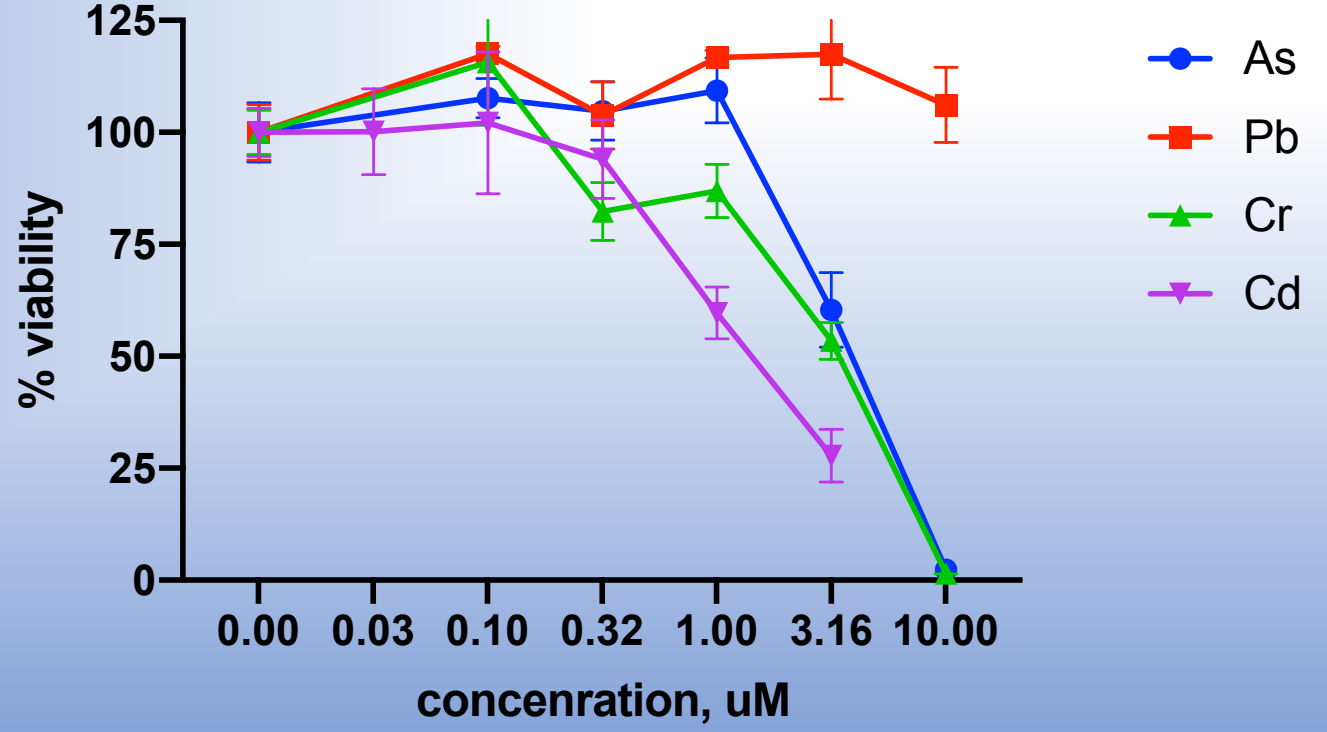
Developmental Neurotoxicity of metal mixture

Lead

Arsenic

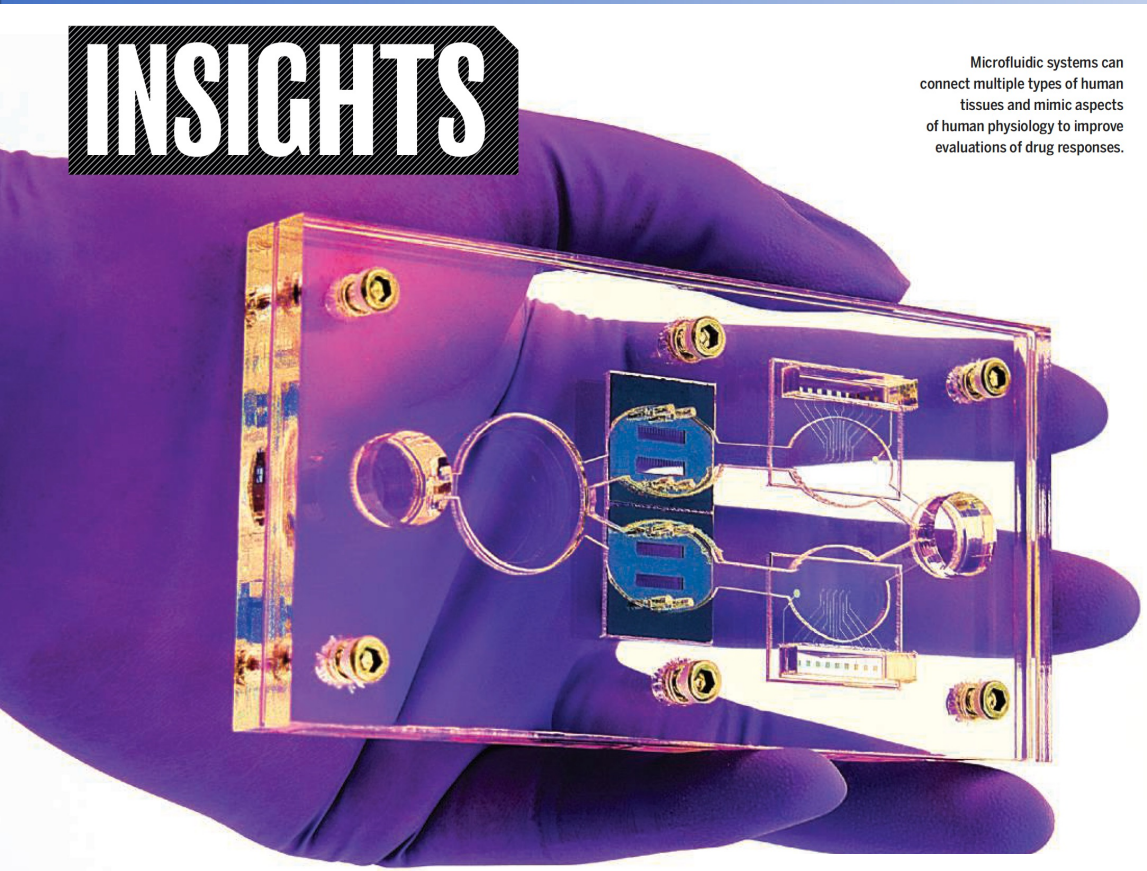
Cadmium

Chromium



Breanne Kincain

Evolution of Cell Culture - high-tech & business opportunity



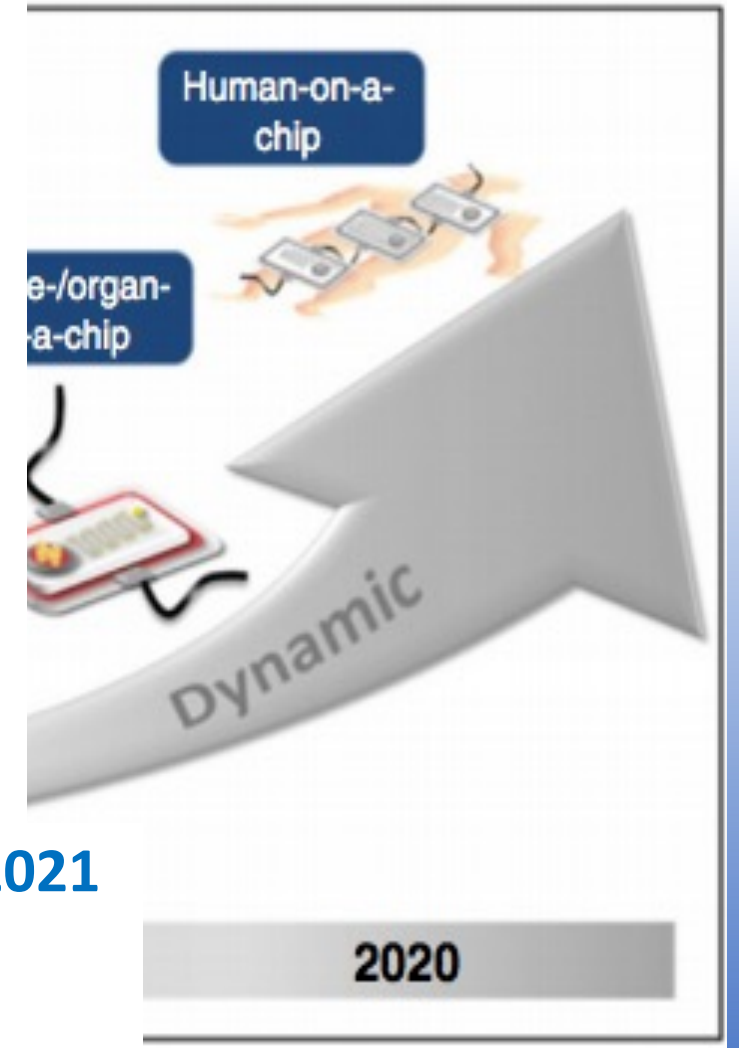
PERSPECTIVES

MEDICINE

Human microphysiological systems for drug development

Organs-on-chips could be used to assess drug efficacy and support personalized medicine

Science 16 Sep 2021



Marx et al., Biology-inspired micro-physiological system approaches to solve the prediction dilemma of substance testing using animals. ALTEX 2016, 33:272-321.

Marx et al., Biology-inspired microphysiological systems to advance medicines for patient benefit and animal welfare. ALTEX 2020, 37:365-394 .

MPS WORLD SUMMIT

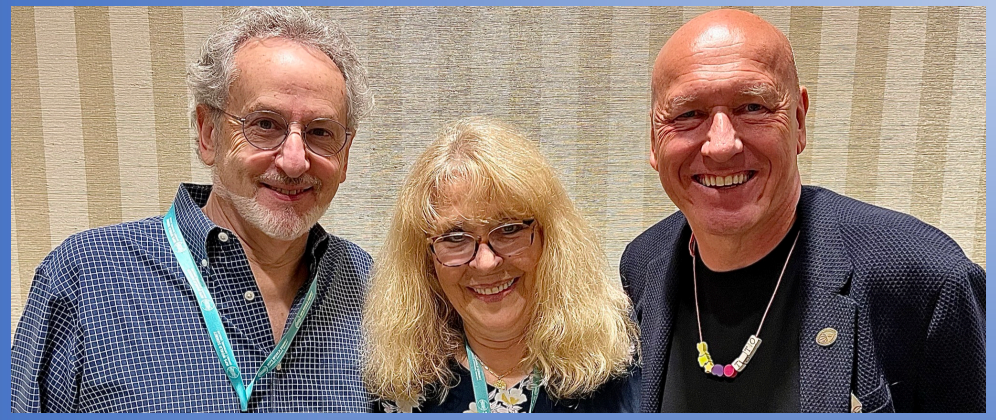
CONNECT, EXCHANGE, EDUCATE

New Orleans 30 May-3 Jun ‘22

Hosts: Suzie Fitzpatrick, FDA

Thomas Hartung, Hopkins

Don Ingber, Harvard



https://mpsworldsummit.com

52 organizations

34 Scientific Advisory Board

665 Registered (215 Online, 65 FDA)

26 Countries

142 speakers, 189 posters

$450k from NCATS

Forming the International MPS Society and Conference Series

2nd MPS World Summit: June 26-30th 2023

Lena Smirnova

Main Organizer

President International MPS Society

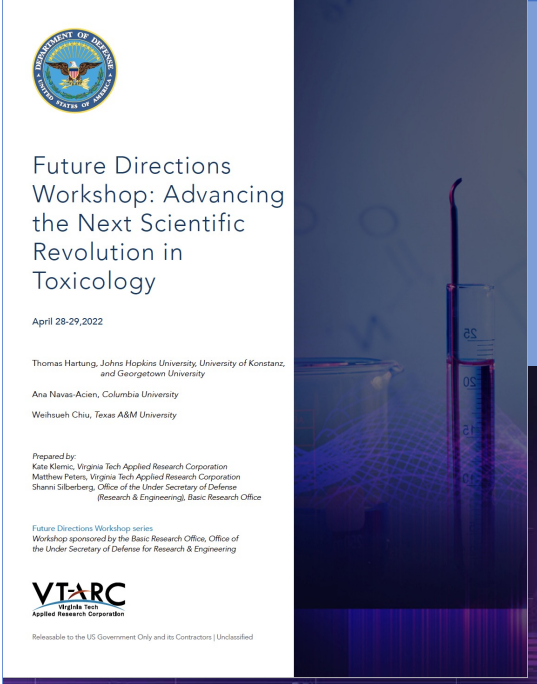
Guidance Document on Good Cell and Tissue Culture Practice 2.0 (GCCP 2.0)

ALTEX 2022, 39:30-70

David Pamies[1], Marcel Leist[2,3], Sandra Coecke[4], Gerard Bowe[4], Dave Allen[5], Gerhard Gstraunthaler[6], Anna Bal-Price[4], Francesca Pistollato[4], Rob deVries[7,8], Helena T. Hogberg[9], Thomas Hartung[2,9] and Glyn Stacey[10,11,12]

- **Quality of cell model (GCCP)**
- **Quality of reporting (GIVReSt)**
- **Quality of results (validation)**

Call for a Human Exposome Project, in press



Co-Chairs

Ana Navas-Acien, Weihsueh A. Chiu & Thomas Hartung

What is emerging that can help us?

Exposure science (high throughput and untargeted exposomics, remote sensing, citizen science …)

Technologies (~omics, high-throughput, MPS, A.I.)

Evidence Integration (Evidence-based Tox, IATA, Green Tox Investigative Tox, Mechanistic Validation, Probabilistic Risk Assessment, Systems Toxicology, virtual experiments…)

A.I. = Making big sense of

Power of computers doubles every 2a

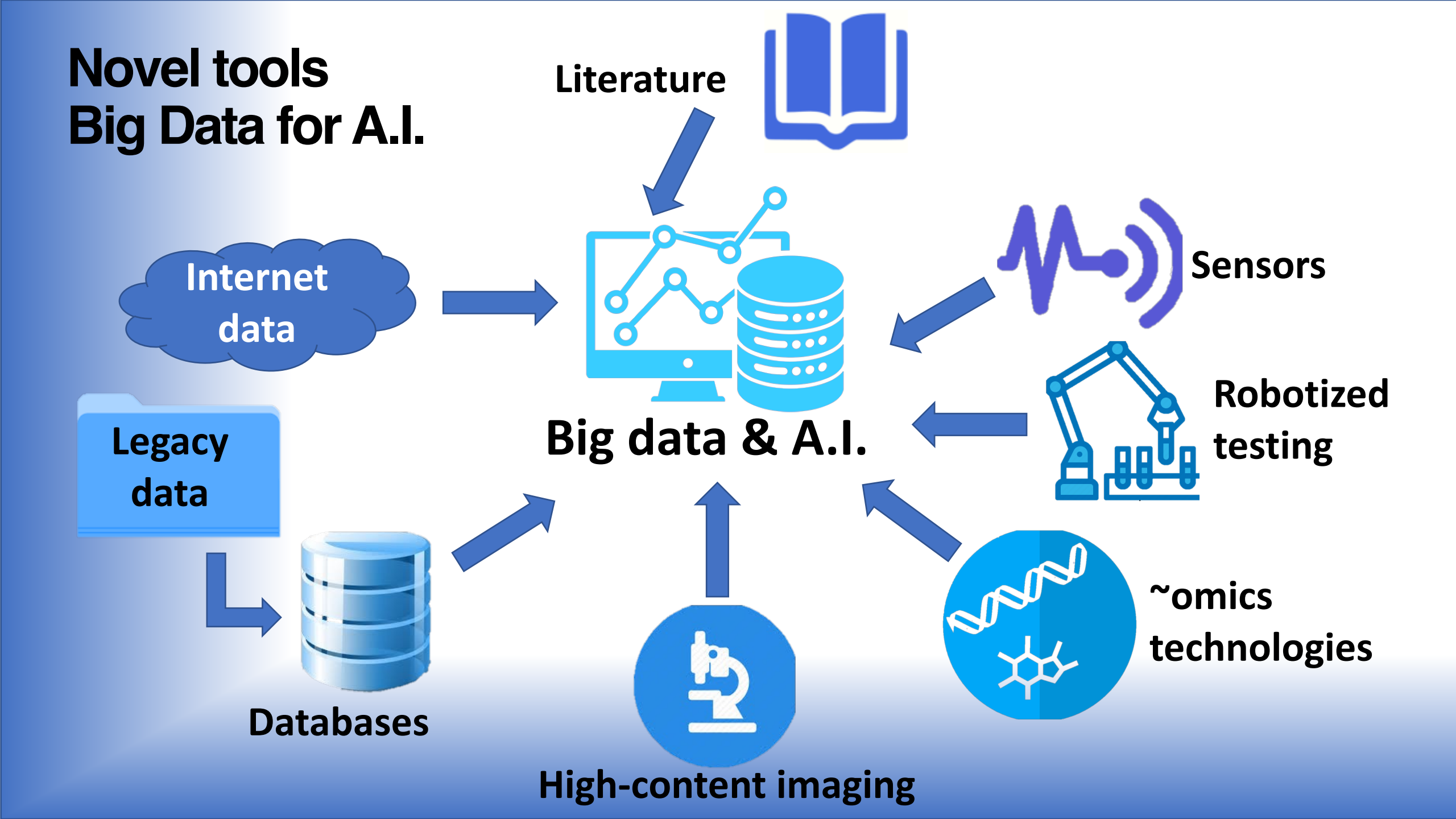
Power of AI doubles every 3 months over last 10a

84% of all data produced last 6a

Natural language processing

https://theamericangenius.com/editorials/big-data-is-watching-you-some-will-panic-others-will-rejoice/

Novel tools
Big Data for A.I.



Tom Luechtefeld

https://sfmagazine.com/technotes/february-2019-wipo-u-s-and-china-lead-the-world-in-ai-innovation/

9 most common toxicity tests

190,000 chemical's hazard cross-validation:

87% correct

ACCEPTED MANUSCRIPT

Machine learning of toxicological big data enables read-across structure activity relationships (RASAR) outperforming animal test reproducibility

Thomas Luechtefeld, Dan Marsh, Craig Rowlands, Thomas Hartung ✉

Toxicological Sciences, kfy152, https://doi.org/10.1093/toxsci/kfy152

Published: 11 July 2018

Science, 12 Feb 2016

TOXICOLOGY

A crystal ball for chemical safety

By comparing new chemicals to known compounds, toxicologists seek early hazard warnings

nature

Legal tussle delays launch of huge toxicity database

Health risks of nearly 10,000 chemicals charted to help predict toxicity of untested substances.

nature

Software beats animal tests at predicting toxicity of chemicals

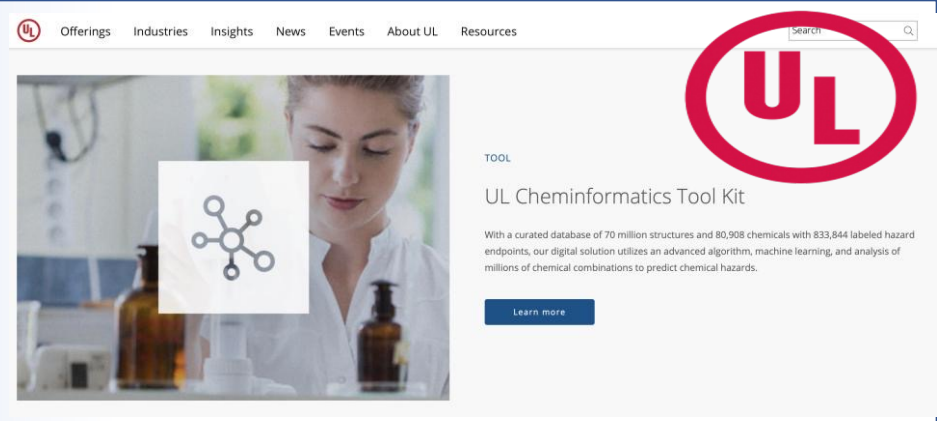
Machine learning on mountain of safety data improves automated assessments.

Science Home News Journals Topics Careers

New digital chemical screening tool could help eliminate animal testing

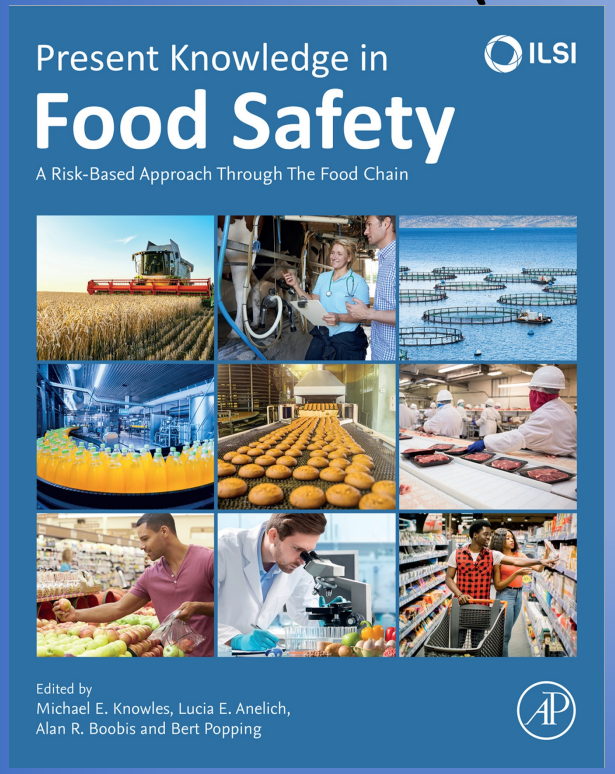
Ongoing RASAR developments

79% (n=131) and 80% (n=375) accuracy in predicting HUMAN skin sensitization (Golden et al., ALTEX, 2020)



38,250 predictions for 4,729 food-relevant substances
83% accurate (n=139) (Fu et al., 2022)

Accepted for Australian Industrial Chemical Legislation 2020



The use of artificial intelligence and big data for the safety evaluation of US food-relevant chemicals

Yuqi Fu[1], Thomas Luechtefeld[1,2], Agnes Karmaus[3] and Thomas Hartung[1,4]

https://www.dreamstime.com/photos-images/sky-limit.html

TABLE 39.1 Five simplified manual curation categorization inventories for 1215 chemicals.

Manual curation categorization	Category number	Chemical count	Percentage
Direct food additive	1	502	39%
Pesticide/residue	3	329	25%
Indirect food additive	2	284	22%
Nonfood	4	106	8%
Not included in manual curation	5	76	6%
		1297[a]	100%

1215 of 4729 chemicals had use categories

TABLE 39.4 Percentage of positive and negative r

egory and toxicity endpoint.

Positivity rate and negativity rate	Direct food additive		Pesticide/residue		Not included in manual curation	
	Positive rate	Negative rate	Positive rate	Negative rate	Positive rate	Negative rate
Acute oral toxicity	28%	72%	54%	46%	37%	63%
Acute dermal irritation	57%	43%	40%	60%	66%	34%
Acute dermal toxicity	20%	80%	43%	57%	33%	67%
Acute aquatic toxicity	16%	84%	59%	41%	11%	89%
Acute inhalation toxicity	24%	76%	47%	53%	34%	66%
Chronic aquatic toxicity	23%	77%	66%	34%	16%	84%
Eye irritation	61%	39%	38%	62%	73%	27%
Mutagenicity	12%	88%	25%	75%	18%	82%
Skin sensitization	34%	66%	51%	49%	42%	58%

Substantial number of hazards

TABLE 39.5 Comparison of RASAR predictions and complementary experimental data classification for high-confidence chemicals.

Chemical	CASRNs	Manual Curation Categorization	Acute Ora Toxicity	Acute Inhalatiion Toxicity	Acute Derma Toxicity	Acute Dermal Irritation	Eye Irritatio	Skin Sensitizatio	Acute Aquati Toxicity	Chronic Aquatic Toxicity	Mutagenicity
Allyl cyclohexanepropionate	2705-87-5	Direct food additive	(0.965) + √- √	(0.922) + √ - √	(0.860) + √ - √	(0.399) - / - √	(0.252) - x - /	(0.928) + √ - √	(0.996) + √ - √	(0.960) + √ - √	(0.059) - x - x
α-phellandrene	99-83-2	Direct food additive	(0.025) - x - √	(0.093) - x - √	(0.039) - x - /	(0.127) - x - √	(0.048) - x - √	(0.905) + √ - √	(0.994) + √ - /	(0.829) + √ - √	(0.060) - x - /
Methyl butyrate	623-42-7	Direct food additive	(0.034) - x - x	(0.185) - x - x	(0.140) - x - /	(0.991) + √ - √	(0.993) + √ - √	(0.132) - x - x	(0.076) - x - /	(0.130) - x - /	(0.161) - x - /
3-(Methylthio)propyl isothiocyanate	505-79-3	Direct food additive	(0.950) + √ - √	(0.818) + √ - √	(0.767) + √ - √	(0.959) + √ - √	(0.941) + √ - √	(0.907) + √ - /	(0.992) + √ - √	(0.919) + √ - √	(0.209) - x - /
Pentachloropyridine	2176-62-7	Indirect food additive	(0.822) + √ - √	(0.980) + √ - √	(0.969) + √ - √	(0.969) + √ - √	(0.945) + √ - √	(0.924) + √ - √	(0.991) + √ - √	(0.902) + √ - √	(0.174) - x - x
Furfural	98-01-1	Indirect food additive	(0.882) + √ - √	(0.949) + √ - √	(0.941) + √ - √	(0.988) + √ - √	(0.991) + √ - √	(0.966) + √ - √	(0.617) + / - √	(0.473) - / - √	(0.872) + √ - √
2,4-Diaminotoluene	95-80-7	Indirect food additive	(0.934) + √ - √	(0.937) + √ - √	(0.990) + √ - √	(0.901) + √ - √	(0.822) + √ - √	(0.983) + √ - √	(0.824) + √ - √	(0.810) + √ - √	(0.987) + √ - √
Dichlorobenzene	106-46-7	Indirect food additive Pesticides/residues	(0.758) + √ - √	(0.796) + √ - √	(0.925) + √ - x	(0.989) + √ - √	(0.974) + √ - √	(0.713) + √ - √	(0.539) + / - √	(0.290) - x - √	(0.903) + √ - x
Coumaphos	56-72-4	Non-food	(0.827) + √ - √	(0.937) + √ - √	(0.892) + √ - √	(0.354) - x - √	(0.278) - x - √	(0.811) + √ - √	(0.996) + √ - √	(0.857) + √ - √	(0.515) + / - x
Coumatetralyl	5836-29-3	Non-food	(0.963) + √ - √	(0.846) + √ - √	(0.837) + √ - √	(0.859) + √ - √	(0.824) + √ - √	(0.938) + √ - x	(0.995) + √ - √	(0.970) + √ - √	(0.518) + / - √
sulfotep	3689-24-5	Non-food	(0.812) + √ - √	(0.780) + √ - √	(0.803) + √ - √	(0.493) - / - √	(0.274) - x - √	(0.577) + / - √	(0.993) + √ - √	(0.907) + √ - √	(0.234) - x - x
2,4-D-1-butyl ester	94-80-4	Non-food	(0.973) + √ - √	(0.984) + √ - /	(0.971) + √ - /	(0.703) + √ - √	(0.590) + / - √	(0.976) + √ - √	(0.984) + √ - √	(0.902) + √ - √	(0.245) - x - x
Terbufos	13071-79-9	Pesticides/residues	(0.648) + / - √	(0.626) + / - √	(0.557) + / - √	(0.490) - / - √	(0.225) - x - √	(0.617) + / - /	(0.998) + √ - √	(0.922) + √ - √	(0.299) - x - x
Tefluthrin	79538-32-2	Pesticides/residues	(0.644) + / - √	(0.822) + √ - √	(0.691) + √ - √	(0.031) - x - √	(0.015) - x - √	(0.065) - x - x	(0.997) + √ - √	(0.971) + √ - √	(0.063) - x - x
Deltamethrin	52918-63-5	Pesticides/residues	(0.831) + √ - √	(0.715) + √ - √	(0.658) + / - /	(0.763) + √ - √	(0.587) + / - √	(0.940) + √ - √	(0.997) + √ - √	(0.907) + √ - √	(0.346) - / - /
Cypermethrin	52315-97-8	Pesticides/residues	(0.556) + / - √	(0.454) - / - √	(0.284) - x - /	(0.059) - x - √	(0.039) - x - √	(0.310) - x - √	(0.996) + √ - √	(0.939) + √ - √	(0.043) - x - x
Fenvalerate	51630-58-1	Pesticides/residues	(0.466) - / - √	(0.039) - x - /	(0.020) - x - /	(0.022) - x - √	(0.016) - x - √	(0.157) - x - √	(0.994) + √ - √	(0.948) + √ - √	(0.021) - x - x
2,5-Dimethylfuran	625-86-5	Not included in manual curation	(0.933) + √ - √	(0.979) + √ - √	(0.975) + √ - /	(0.996) + √ - √	(0.996) + √ - √	(0.975) + √ - √	(0.595) + / - /	(0.514) + / - /	(0.821) + √ - x

Small subset compared to literature findings:

83% correct

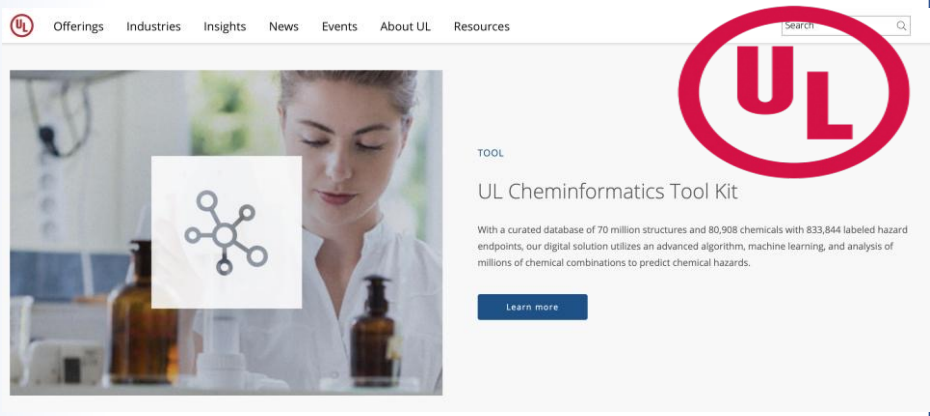
Ongoing RASAR developments

79% (n=131) and 80% (n=375) accuracy in predicting HUMAN skin sensitization (Golden et al., ALTEX, 2020)

38,250 predictions for 4,729 food-relevant substances
83% accurate (n=139) (Fu et al., 2022)

Preliminary (Luechtefeld et al., in preparation):
Reproductive Tox 82% accurate (n=1152)
Carcinogenicity 75% accurate (n=950)
Androgen effect 98% accurate (n=8492)
Estrogen transactivation 80% accurate (n=1660)

EU ONTOX project ($20 million, 2021-2026) to expand to liver, kidney and developing brain



Accepted for Australian Industrial Chemical Legislation 2020

https://www.dreamstime.com/photos-images/sky-limit.html

The challenge

https://www.loopclosed.com.au/program_services/data_integration_and_analysis.html

Similar for

- Systematic reviews
- Risk assessments
- Integrated Testing Strategies

http://phd.dia.uniroma3.it/multi-source-data-integration-with-humans-in-the-loop/

In vivitrosi

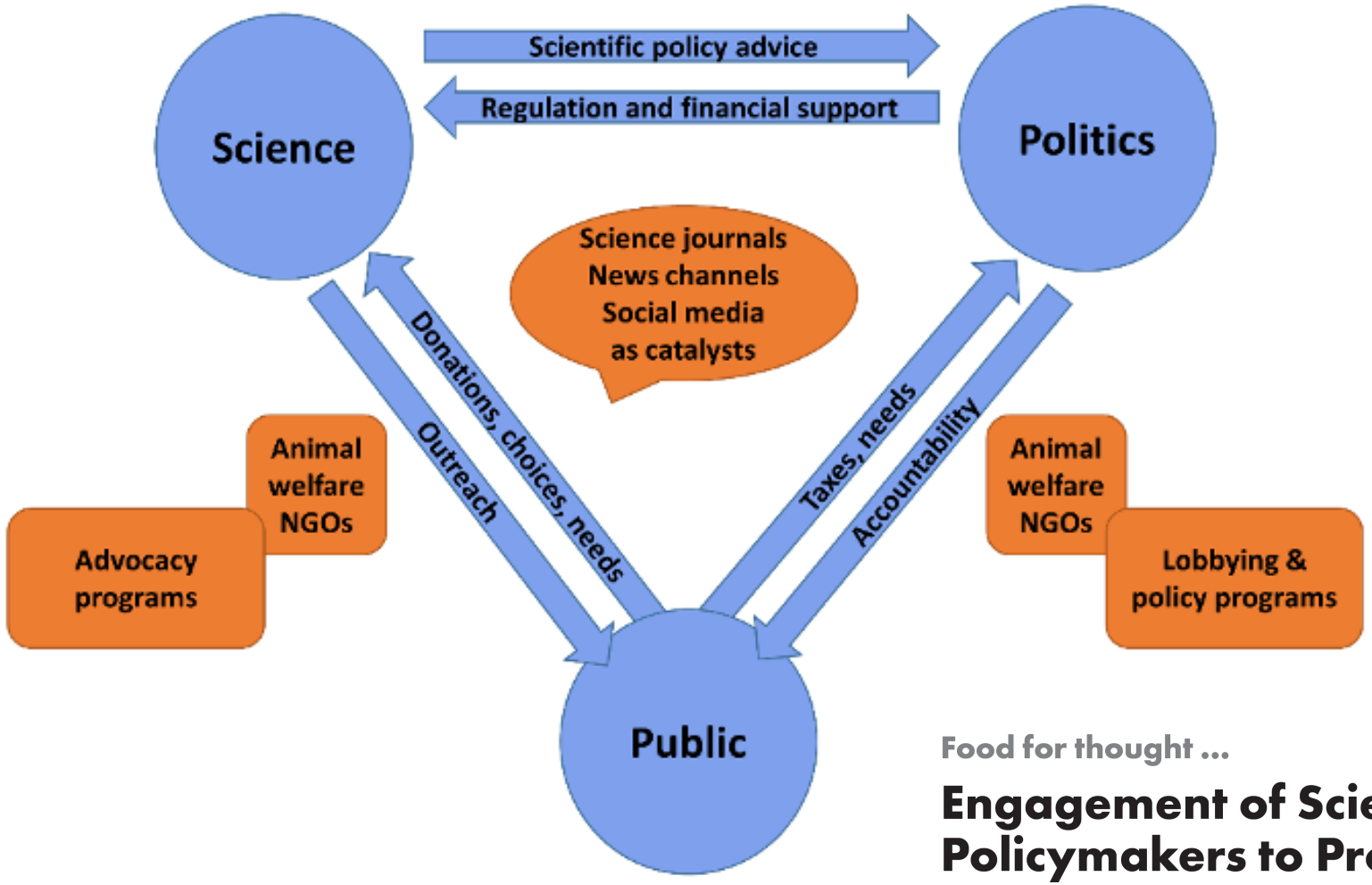
Replacement of animal testing by integrated approaches to testing and assessment (IATA): a call for in vivitrosi

Francesca Caloni[1] · Isabella De Angelis[2] · Thomas Hartung[3,4]

Arch Toxicol 2022

Aka Integrated Testing Strategies, IATA, Defined Approaches…

CAAT as 'lubricant' in these interactions



Food for thought ...

Engagement of Scientists with the Public and Policymakers to Promote Alternative Methods

Sonja von Aulock[1], Francois Busquet[2,3], Paul Locke[4], Kathrin Herrmann[4,5] and Thomas Hartung[2,4]

Almost 16,000 active learners

Since 2018

Toxicology 21:
Scientific Applications

Johns Hopkins University

8500+ enrolled learners

Since 2019

Evidence-based
Toxicology

Johns Hopkins University

7000+ enrolled learners

coursera

Massive Open Online Courses platform

The difficulty lies not in the new ideas,

but in escaping from the old ones.

JM Keynes

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