

A personal perspective about endocrine disruptors in Switzerland



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1. From Wingspread to the NFP 50

- Theo Colborn's Great Lakes survey: developmental, behavioral, reproductive and endocrine alterations in fishes, birds and mammals (1990).
- If these anomalies were due to the hormonal effects of already banned environmental chemicals (DDT, PCB) there was nothing to do except to wait until further lowering of the toxicant levels.
- Instead, an accident in our laboratory at that time revealed that there were xenoestrogens in the environment that were yet to be regulated.



***p*-Nonyl-Phenol: An Estrogenic Xenobiotic Released from “Modified” Polystyrene**

Alkylphenols are widely used as plastic additives and surfactants. We report the identification of an alkylphenol, nonylphenol, as an estrogenic substance released from plastic centrifuge tubes. This compound was extracted with methanol, purified by flash chromatography and reverse-phase high performance liquid chromatography, and identified by gas chromatography-mass spectrometry. Nonylphenol induced both cell proliferation and progesterone receptor in human estrogen-sensitive MCF₇ breast tumor cells. Nonylphenol also triggered mitotic activity in rat endometrium; this result confirms the reliability of the MCF₇ cell proliferation bioassay. The estrogenic properties of alkylphenols, specifically nonylphenols, indicate that the use of plasticware containing these chemicals in experimental and diagnostic tests may lead to spurious results, and these compounds as well as alkylphenol polyethoxylates may also be potentially harmful to exposed humans and the environment at large.

Soto AM, Justicia H, Wray JW, Sonnenschein C. *p*-Nonyl-phenol: an estrogenic xenobiotic released from "modified" polystyrene. *Environ Health Perspect.* 1991, 92:167-73.

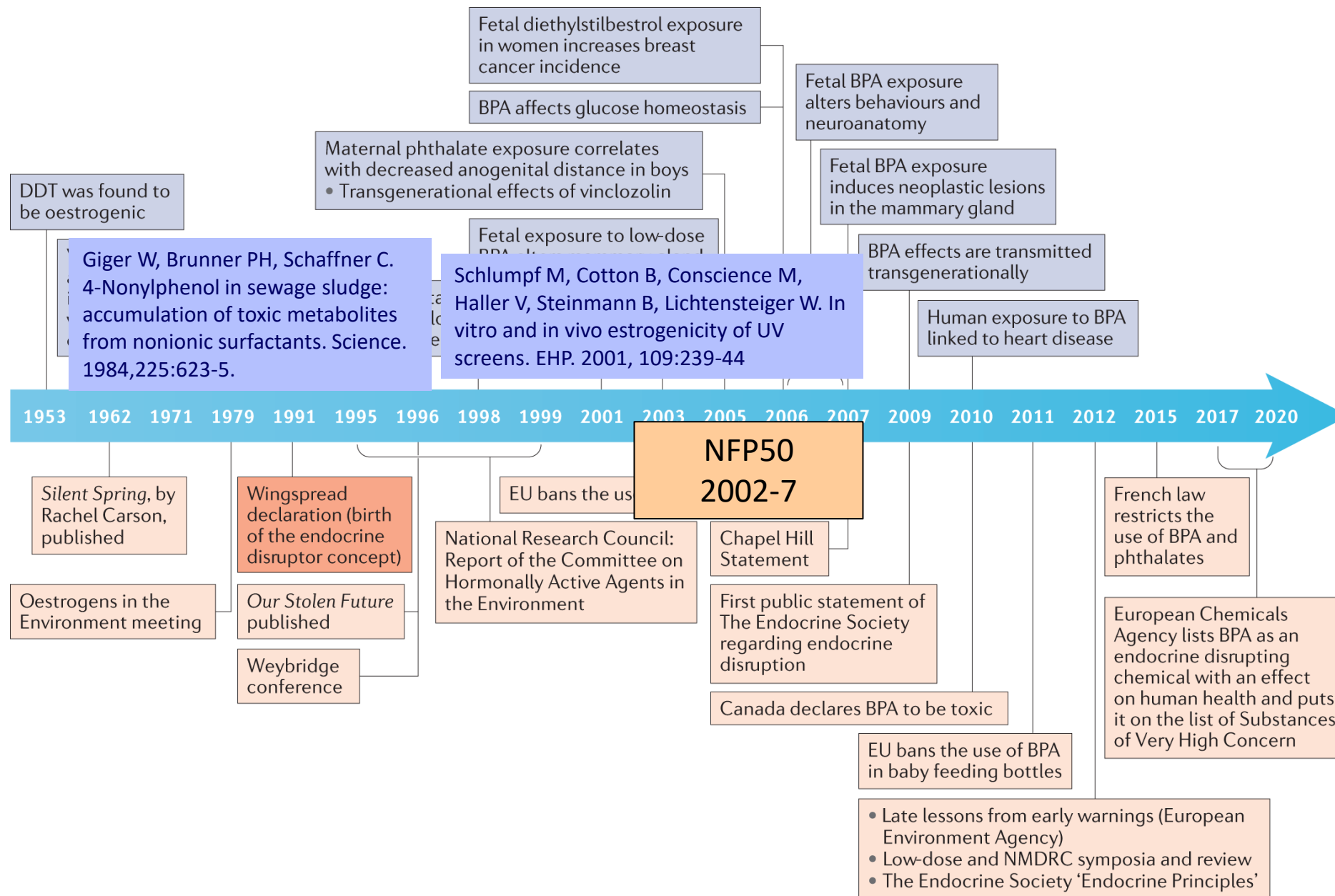
***p*-Nonyl-Phenol: An Estrogenic Xenobiotic Released from “Modified” Polystyrene**

“... are alkylphenols a likely cause of environmental hazard due to their estrogenicity? Alkylphenol was found in PVC used in the food processing and packaging industries (26). **Nonylphenol may leach from plastic and was reported to contaminate water flowing through PVC tubing** (16). The annual production of *p*-nonylphenol in the U.S. was 45,000 tons in 1976 (27). Nonylphenols are also used in the synthesis of surfactants such as nonoxyphenol, a compound present in intravaginal spermicides (28) and alkylphenol polyethoxylates used as industrial detergents (29). The annual production of alkylphenol polyethoxylates in the U.S. was 140,000 metric tons in 1982 (29). **Although these detergents are unlikely to have estrogenic activity, they are known to be degraded to free nonylphenol in rodent models (3) as well as in sewage sludge (31). Anaerobically stabilized sludge samples were reported to contain 0.45 to 2.53 g *p*-nonylphenol/kg (31).”**

4-Nonylphenol in Sewage Sludge: Accumulation of Toxic Metabolites from Nonionic Surfactants

Abstract. *Anaerobically treated sewage sludge was found to contain extraordinarily high concentrations of 4-nonylphenol, a metabolite derived from nonionic surfactants of the nonylphenol polyethoxylate type. Concentrations in activated sewage sludge, in mixed primary and secondary sludge, and in aerobically stabilized sludge were substantially lower, suggesting that the formation of 4-nonylphenol is favored under mesophilic anaerobic conditions. Because 4-nonylphenol may be highly toxic to aquatic life, further research is needed on the fate of 4-nonylphenol after sludge is disposed of in the environment.*

Giger W, Brunner PH, Schaffner C. 4-Nonylphenol in sewage sludge: accumulation of toxic metabolites from nonionic surfactants. *Science*. 1984 Aug 10;225(4662):623-5. doi: 10.1126/science.6740328. PMID: 6740328.



2. A brief introduction to the NRP ‘Endocrine Disruptors’

1. I was asked to talk about my personal experience as a member of the Steering Committee of the NFP 50.
2. I would like to thank Dr. Barbara Flückiger Schwarzenbach and Professor Felix Althaus for providing NFP50 documents to help my memory, slide presentations on this subject and answering assorted queries about what happened after the conclusion of the program. I also would like to stress that Margret Schlumpf and Walter Lichtensteiger played an important role on the creations of the NFP50 program.
3. The slides I borrowed from them can be recognized because of their design, like this one.

Objectives of NRP 'Endocrine Disruptors'

The National Research Programme 'Endocrine Disruptors' aims

- _ to develop scientific strategies to assess the risks and hazards of endocrine disruptors
- _ to define a set of rules for future development of pertinent substances
- _ to create consensus platforms for science, industry and authorities to avoid the negative impact of endocrine disruptors
- _ 5-year period: 2002 – 2007
- _ Funding: 15 million CHF

The NRP 50 in a Nutshell

International Steering Committee

President: Professor Dr. Felix R. Althaus

Members:

Dr. Susan Jobling, Dept. of Biological Sciences, Brunel University, Uxbridge, England

Prof. Konrad Hungerbühler, Institute for Chemical and Bioengineering, Safety & Environmental Technology Group, ETHZ, Zurich (2005 – end of programme)

Prof. Michael Oehme, Analytische organische Chemie, Universität Basel (2001 – 2005; substituted by K. Hungerbühler)

Prof. Urs T. Rüegg, Professor of Pharmacology, School of Pharmacy, University of Geneva

Prof. Ana Soto, Department of Anatomy and Cellular Biology, Boston, USA

Dr. Christoph Studer, Federal Office for the Environment, Berne

Prof. Joseph G. Vost†, Laboratory of Pathology and Immunobiology, National Institute of Public Health and the Environment, Bilthoven, The Netherlands (2001-2006)

Objectives of the NRP 'Endocrine Disruptors'

Implementation Officer: Dr. Marcel Trachsel, int/ext Communications AG, Basel

Delegate of the Research Council, Div. IV: Prof. Isabel Roditi, Institute of Cell Biology, University of Berne

Program coordinator: Dr. Barbara Flückiger Schwarzenbach, Secretariat of Div. IV, SNSF

The members of the Steering Committee met in nine meetings to draw up the implementation plan, to discuss and evaluate the submitted research proposals as well as progress and final reports. Site visits were conducted on all groups of the first call after about two years of research. In addition to the scientific steering of the program, many hours were devoted to various aspects of implementation such as the consensus platforms.

_ 30 approved research projects in three phases

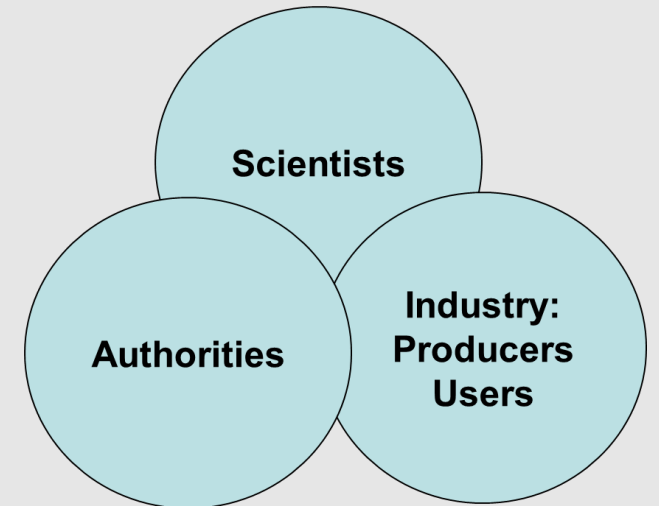
NRP 50 Consensus Platforms

_ Definition

- _ A stepwise moderated issue-driven constructive non-public debate among scientists, industrial decision makers (producers and users) and decision makers from involved authorities.

_ Objectives

- _ Create the best general agreement upon
 - _ the impact of endocrine disruptors on humans, animals and ecosystems
 - _ a set of rules for handling and future development of these substances.



Results of the NRP 50 program

Semen quality of young men in Switzerland: a nationwide cross-sectional population-based study

ABSTRACT

Background: Sperm counts have been steadily decreasing over the past five decades with regional differences in the Western world. The reasons behind these trends are complex, but numerous insights indicate that environmental and lifestyle factors are important players.

Objective: To evaluate semen quality and male reproductive health in Switzerland.

Materials and methods: A nationwide cross-sectional study was conducted on 2523 young men coming from all regions of Switzerland, recruited during military conscription. Semen volume, sperm concentration, motility, and morphology were analyzed. Anatomy of the genital area and testicular volume was recorded. Testicular cancer incidence rates in the general population were retrieved from Swiss regional registries.

Results: Median sperm concentration adjusted for period of sexual abstinence was 48 million/mL. Comparing with the 5th percentile of the WHO reference values for fertile men, 17% of men had sperm concentration below 15 million/mL, 25% had less than 40% motile spermatozoa, and 43% had less than 4% normal forms. Disparities in semen quality among geographic regions, urbanization rates, and linguistic areas were limited. A larger proportion of men with poor semen quality had been exposed in utero to maternal smoking. **Furthermore, testicular cancer incidence rates in the Swiss general population increased significantly between 1980 and 2014.**

Discussion: For the first time, a systematic sampling among young men has confirmed that semen quality is affected on a national level. **The median sperm concentration measured is among the lowest observed in Europe.** No specific geographical differences could be identified. Further studies are needed to determine to what extent the fertility of Swiss men is compromised and to evaluate the impact of environmental and lifestyle factors.

Conclusion: A significant proportion of Swiss young men display suboptimal semen quality with only 38% having sperm concentration, motility, and morphology values that met WHO semen reference criteria.

Results of the NRP 50 programme (from final report)

The NRP 50 results highlight the potential risks of human exposure, and if animal studies are taken at face value, early gestational exposure may contribute to fetal-origin-late-onset-adult-disease' in other major areas, such as cancer, obesity, diabetes, urogenital disorders and fertility.

NRP 50 research brought forward new chemicals as endocrine disruptors (e.g. UV filters), new targets (such as corticoid receptor signaling or PPAR), and new detection methods (mass spectrometry, high density oligonucleotide microarrays, in silico prediction).

NRP 50 research identified potential routes of exposure (breast milk, food intake and aqueous environment) and factors affecting the environmental processing of endocrine disruptors.

Finally, integrative risk assessment techniques allowed for the identification of hot spot chemicals in the environment as well as the exclusion of others.

UV filters: a Swiss discovery

Durrer S, Maerker K, Schlumpf M, Lichtensteiger W. Estrogen target gene regulation and coactivator expression in rat uterus after developmental exposure to the ultraviolet filter 4-methylbenzylidene camphor. *Endocrinology*. 2005 May;146:2130-9.

Maerker K, Lichtensteiger W, Durrer S, Conscience M, Schlumpf M. Sex- and region-specific alterations of progesterone receptor mRNA levels and estrogen sensitivity in rat brain following developmental exposure to the estrogenic UV filter 4-methylbenzylidene camphor. *Environ Toxicol Pharmacol*. 2005 May;19:761-5.

Maerker K, Durrer S, Henseler M, Schlumpf M, Lichtensteiger W. Sexually dimorphic gene regulation in brain as a target for endocrine disruptors: developmental exposure of rats to 4-methylbenzylidene camphor. *Toxicol Appl Pharmacol*. 2007 Jan 15;218:152-65.

Durrer S, Ehnes C, Fuetsch M, Maerker K, Schlumpf M, Lichtensteiger W. Estrogen sensitivity of target genes and expression of nuclear receptor co-regulators in rat prostate after pre- and postnatal exposure to the ultraviolet filter 4-methylbenzylidene camphor. *Environ Health Perspect*. 2007 115: Suppl 142-50.

Faass O, Schlumpf M, Reolon S, Henseler M, Maerker K, Durrer S, Lichtensteiger W. Female sexual behavior, estrous cycle and gene expression in sexually dimorphic brain regions after pre- and postnatal exposure to endocrine active UV filters. *Neurotoxicology*. 2009 Mar;30:249-60.

A very relevant entity grew out of the NFP50: the FPF

Jane Muncke obtained her PhD degree at the Swiss Federal Institute of Technology Zurich (ETHZ). During her graduate and postgraduate work at the Swiss Federal Institute of Aquatic Science and Technology (EAWAG); she worked in one of the labs supported by the NFP50.

- The FPF output of databases, research papers, reviews, commentaries and interactions with government and industry represent a substantial body of useful work.

- Parkinson LV, Geueke B, Muncke J found that of the 921 substances that are potential mammary carcinogens, “...that 189 (21%) of the potential mammary carcinogens have been measured in FCMs. When limiting these results to migration studies published in 2020-2022, 76 potential mammary carcinogens have been detected to migrate from FCMs sold in markets across the globe, under realistic conditions of use. This implies that chronic exposure of the entire population to potential mammary carcinogens from FCMs is the norm and highlights an important, but currently underappreciated opportunity for prevention” (Potential mammary carcinogens used in food contact articles: implications for policy, enforcement, and prevention. Front Toxicol. 2024 Sep 24;6:1440331).

Regulation moves at geological time speed

1. Science and society

- *Conflict of interest*
- *Lobbying*
- *Agnotology*
- *Outdated regulatory science*

2. Inside Science

- Theoretical crisis
- Science for the sake of science vs applied science



Why researchers let the «merchants of doubt» set the agenda?

“It is premature to regulate before all the mechanistic details are known”.

This call to do more research is appealing to experimentalists particularly those that adhere to reductionism, but also those that are sensitive to organicism and try to provide alternatives to putative mechanisms.

The endocrine disruptor community knows that there is sufficient evidence to act now. Regardless of one's theoretical preferences researchers discriminate between science for its own sake (time is not of the essence) and applying science to the benefit of society (immediate action).

Soto, A.M., and Sonnenschein, C. Endocrine disruptors - putting the mechanistic cart before the phenomenological horse. Nat Rev Endocrinol 14: 317-8, 2018.

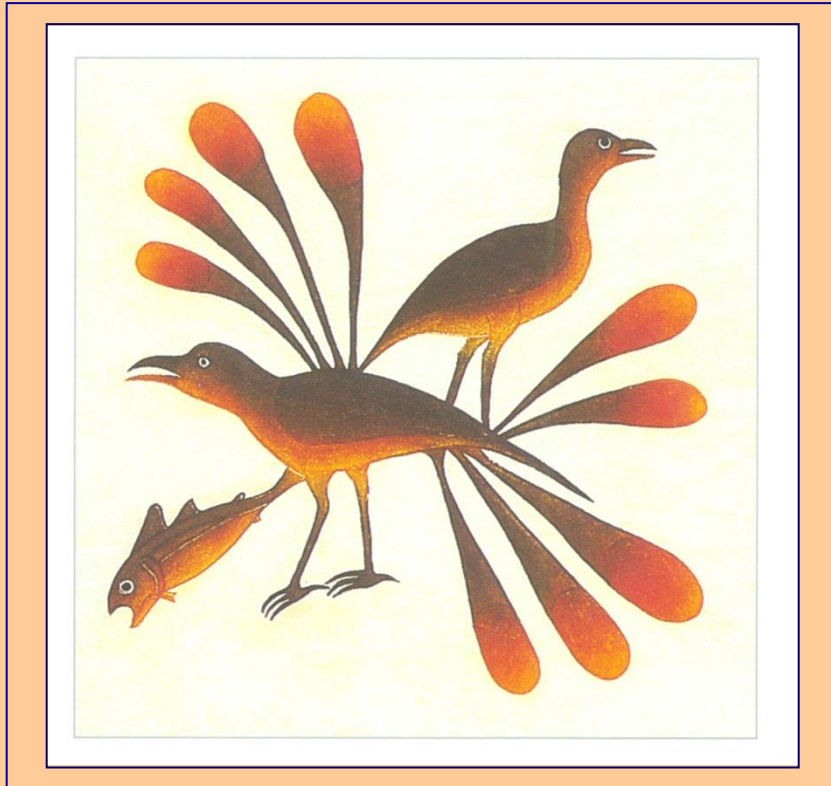
Soto, A.M., and Sonnenschein, C. From evidence of harm to public health policy: is there light at the end of the tunnel? A Commentary on "Update on the health effects of bisphenol A: Overwhelming evidence of harm" Endocrinology. 162 (3), 2020.

Light at the end of the tunnel?

- On October 14, 2020, the European Commission published a chemicals strategy for sustainability. It proposes “**to establish legally binding hazard identification of endocrine disruptors**, based on the definition of the WHO, building on criteria already developed for pesticides and biocides, and apply it across all legislation; **ensure that endocrine disruptors are banned in consumer products as soon as they are identified.**” This great step forward is the result of the efforts of scientists, journalists, politicians and medical and scientific societies like ours.
- Not surprisingly, resistance from the “usual suspects” is already materializing. Endocrinologists should be ready to oppose the delaying tactics armed with a clear understanding of when “enough is enough”. See for example Le Monde, September 27(*Diving into the black box of global pesticide propaganda*) ,28 (*Investigation reveals mass profiling of 'opponents' of the agrochemical industry*), and 29 (*How Trump's administration tried to torpedo the EU Green Deal using influence and misinformation campaigns*),2024 issues (S. Foucart, E. DeBre M. Gibbs).

Biology should again embrace theorization

- **While there is a theory about the “long timescale” (evolution, phylogenesis), a theory about the “short timescale” (life cycle, ontogenesis) is beginning to be constructed taking into consideration the organisms as agents, not just the passive subjects of natural selection** (Walsh, D. “Organisms, Agency, and Evolution”, 2015, Soto AM et al. “Toward a theory of organisms: Three founding principles in search of a useful integration”. PBMB 122:77-82, 2016, Montévil M, Mossio M. *The Identity of Organisms in Scientific Practice: Integrating Historical and Relational Conceptions*. Front Physiol. 2020 Jun 17;11:611. doi: 10.3389/fphys.2020.00611. PMID: 32625111; PMCID: PMC7311753).
- **Regarding endocrinology it is urgent to develop proper theoretical principles to provide a useful framework both for experimentation and for explaining the phenotypes arising from endocrine disruption** (Bich L, Mossio M, Soto AM. “Glycemia regulation: From feedback loops to organizational closure”. Front Physiol 11:69, 2020).
- **Theorization is also necessary to buttress empirical results and to provide means to close uncertainty gaps that can be exploited to slow the march of the “merchants of doubt.”**



Acknowledgements:

I would like to thank Dr. Barbara Flückiger Schwarzenbach and Professor Felix Althaus for providing NFP50 documents to help my memory, slide presentations on this subject and answering assorted queries about what happened after the conclusion of the program.

I would also like to thank Dr. Jane Muncke for inviting me to talk about the NFP50 from a personal perspective.

Disclosure:

I am not a professional historian-do not blame me if I missed relevant points regarding the NFP50 achievements.