CHEMICAL DISINFECTION FROM THE PERSPECTIVE OF EMERGING & NEWLY IDENTIFIED HEALTH RISKS

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« Global Hygiene Strategies for Health Care facilities with special regards to chemical disinfection »

Rudolf Schülke Stiftung Hamburg 2018

Disinfection: Newly Identified Health Risks ?

- QUESTIONS OF DEFINITIONS
- ANTI -MICROBIAL RESISTANCE
- ENVIRONMENTAL & HUMAN TOXICITY

DEFINITIONS (1)

- Regulation (EU) 528/2012 improves the functioning of the single market while ensuring a high level of protection for human health, animal health and the environment,
- The Regulation sets out rules for approving active substances, authorising the selling and the use of biocidal products and selling articles treated,
- A provision of dual use is intended to adress the case of biocidal products have a dual function (ex. plant protection and biocide) but the situation is not yet really clear between antiseptics and disinfectants for human cares.

DEFINITIONS (2)

- The process includes both National Autorisation, Mutual Recognition and Union Autorisation for biocidal product/ biocidal family with similar conditions of use across the Union, except those containing active substances meeting the exclusion criteria and certain product-types (14,15,17,20 and 21)
- Depending upon the product-types, Union autorisation will be available in 3 different stages,

  from 1/09/2013 for product-types 1,3, 4, 5, 18 and 19,

  from 1/01/2017 for product-types 2, 6 and 13,

  from 1/01/2020 for product-types 7, 8, 9,10, 11, 12, 16 and 22.

DEFINITIONS (3)

- Depending of the intended application (and the country !!) skin disinfectants may fall under different legal frameworks because, within the European Union, the classification is not uniform.
- The Commission recognised that a clear distinction between the Biocidal Products Directive 98/8/EC and the Human Medicinal Products Directive 2001/83/EC is a crucial issue and that, for the borderline products, there is a need to give practical guidance and examples.
- In accordance with article 2(2) of the MDP Directive, this directive shall apply when a medicinal product is covered by other Community legislation.

DEFINITIONS (4)

- ECHA stated in february 2017 that products for disinfection of damaged or undamaged skin are always medicinal products covered by the Directive 2001/83/EC, but in may 2017 the Commission answered to a parliamentary question that they are biocidal products and that a biocidal product for skin disinfection can be authorised provided it is safe for patients.
- These legal definitions are not interpreted uniformly by the MS; in some countries this is not clear: disinfectants and antiseptics(biocidal products) for both intact and damaged skin, or disinfectants and antiseptics considered as medicinal products ?
- Many biocidal products do not have a marketing autorisation under the legislation regulating medicinal products.

DEFINITIONS (5)

- The differences are registration, manufacturing and quality control under GMPs, medical indications and pharmacovigilance.
- Does it may induce harm effects in patients and healthcare workers as claimed by some NGOs ?
- These NGOs are calling the Commission for issuing guidelines on the differences between biocidal and medicinal products regarding the classification of disinfectants (or antiseptics ?) for the safest antisepsis of the skin.

DEFINITIONS (6)

NOTIFICATIONS OF UNEXPECTED OR ADVERSE EFFECTS

Article 47 of EU BPR places a duties on all Autorisation holders to make known to Competent Authorities, the European Commission and ECHA any new information of which they are aware, or may reasonably expected to be aware, concerning the biocidal product or the active substance in that product which is relevant to, and may affect, the autorisation.

For instance, any new information relating to the hazardous properties or the development of resistance to the active substance or the biocidal product, changes in composition of the product or in packaging ….

ANTI-MICROBIAL RESISTANCE (1)

- In 2009 the former European Commission SCENIHR produced an opinion dealing with the possibility of some disinfectants and their misuse to facilitate or increase antibiotics resistance.
- In 2017 the European Commission launched a new AntiMicrobial Resistance action plan with the aim to:
    - make the EU a best practice region,
    - boost research and development,
    - shape the global agenda for fulfilling these goals.

On the 5th of january 2018 in Brüssels took place the second meeting of the UE One-Health Network on AMR !

ANTI-MICROBIAL RESISTANCE (2)

- The possibility for disinfectants to induce or increase AMR is very actual with pros (e.g. E. Larson) and contras (e.g. S. Bloomfield, B. Rutala) with a lot of recent papers.
- No doubt it is possible to induce « resistance » to disinfectants » in vitro », but not clear « in situ ».
- Problem of vocabulary between researchers: what is resistance, coresistance, tolerance, decreased sensibility ? according to which methodology, including the VBNC microorganisms and the role of biofilm for protecting the cells !!!

ANTI-MICROBIAL RESISTANCE (3)

- The last issued paper by Kim & Wood (Tolerant, growing cells from nutrients shifts are not persister cells; mBio march/april 2017, 8, 2) is trying to make the situation more clear:
- Persisters are the remaining genetically unaltered population of bacterial cells that, after an initial die-off, survive prolonged antibiotic treatment with a basically unchanging or slowly decreasing population density due to their lack of metabolic activity,
- Resistant cells grow in the presence of the antibiotic due to mutations,
- Tolerant cells grow prior to antibiotic addition and then survive longer than exponentially growing cells in the presence of the antibiotic but their population usually continues to decrease appreciably and the phenotype is a population-wide phenomenon.

ANTI-MICROBIAL RESISTANCE (4)

- Some labs are studying metabollically active and growing cells populations (e.g. as a result of nutrients shifts) and attributing the phenopytpes they discern to persister cells while other labs are studying dormant cells.
- Kim & Wood argue that the metabollically active cell population should more accuratly be considered tolerant cells, while the dormant cells are the true persister population with lack of transcription, translation and reduced metabolic activity.
- The molecular mechanism underlying bacterial persisters were described by E. Maisonneuve & K. Gerdes (Cell 2014, 157, 539-548)

ANTI-MICROBIAL RESISTANCE (5)

- No more doubt that drug persistence is a widespread phenomenon in which a subpopulation is able to survive antimicrobial treatment without acquiring resistance-conferring genetic changes,
- Persistence is, according to N.R. Cohen & al., an actively maintained state triggered and enbled by a network of intracellular stress that can accelerate processes of adaptative evolution (Cell Host & Microbe, 2013, 13, 632-642).
- They are a lot of papers demonstrating this is possible with many disinfectants. Less papers describe also a simultaneous antibiotic resistance of these cells.

ANTI-MICROBIAL RESISTANCE (6)

- Due to the similarity between the mechanisms of resistance against antibiotics and disinfectants (target modification, over-expression of the target, reduction of permeability, efflux pumps..) it is not surprising to isolate mutants resistant to both antimicrobials,
- This is especially described for Triclosan, Chlohexidine, Quats and mercury salts,
- After the first alert by A.E. Aiello & E. Larson (Lancet Inf. Dis. 2003, 3(8), 501-506) numerous papers have described the simultaneous resistance to AB and Triclosan until the recent demonstration by M.A. Webber et al. of a relation between the resistance to quinolones (quinolone-resistant gyrase mutants) and a decreased sensibility to Triclosan (J. Antimicr. Therapy, 2017; DOI: 10.1093/jac/dkx201).
- An other recent paper of Y.H. Huang et al. describes a specific Triclosan Enoyl-acyl-carrier protein reductase (FabV) in Pseudomonas (Front. Microbiol. 2017 DOI 10. 3389/fmrib.2016.011903).

ANTI-MICROBIAL RESISTANCE (7)

- The occurrence of a common «resistance » against antibiotics and some Quats or mercury salts is well described.
- The situation is not so clear for Chlorhexidine but a recent paper of J.C. McNeil et al. describes such a situation for Staphylococcus in ICUs (Antimicr. Agents & Chemotherapy, 2016, 60(2),).
- Thus it is not surprisingly that specialists and NGO’s are calling for a prudent use both for antibiotics and disinfectants since, until now, there is no clear demonstration of the occurence in situ of the emergence of AB-resistant microorganisms in the general environment even it has been described in very specific environments like during disinfection of instruments in hospitals.
- This is the purpose of the actual BTSF european program.

TOXICITY (1)

- The Regulation (EU) 528/2012 contains criteria which have been set in order to phase out the use of substances of very high concern and to ensure that, over time, better alternatives are used instead of these substances, this includes:

- Substances classified as: carcinogens category 1A or 1B
  mutagens category 1A or 1B
  toxic for reproduction category 1A or 1B
  persistent, bio-accumulative and toxic
  endocrine disruptors

TOXICITY (2)

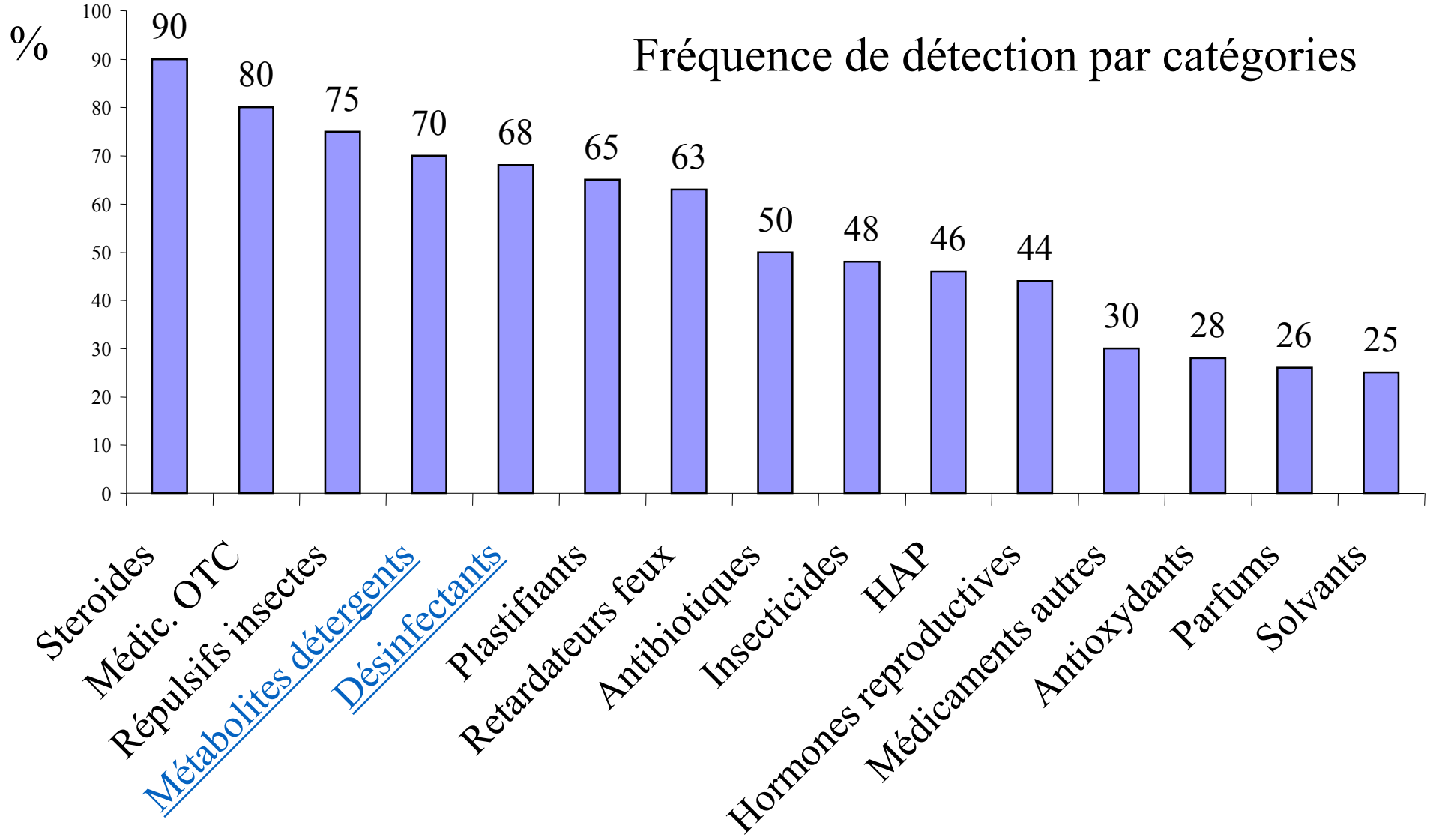
ENVIRONMENTAL TOXICITY

After a workshop in Germany in 2012, organized by the Federal Environmental Agency and the network NORMAN, the following points were hightlighted:

- biocides can be found in relevant concentrations in the environment,
- many single findings prove that the use of biocides can cause environmental burdens,
- about 60% of the prioritized biocides are not appropriately monitored because of the lack of adequate methodology,
- data of production and use amounts of biocides are lacking,
- research and cooperation between stakeholders should be enhanced.

ÉTUDE USGS sur 139 sites USA

Kolpin *et al.* Environm. Sci. Technol. 2002



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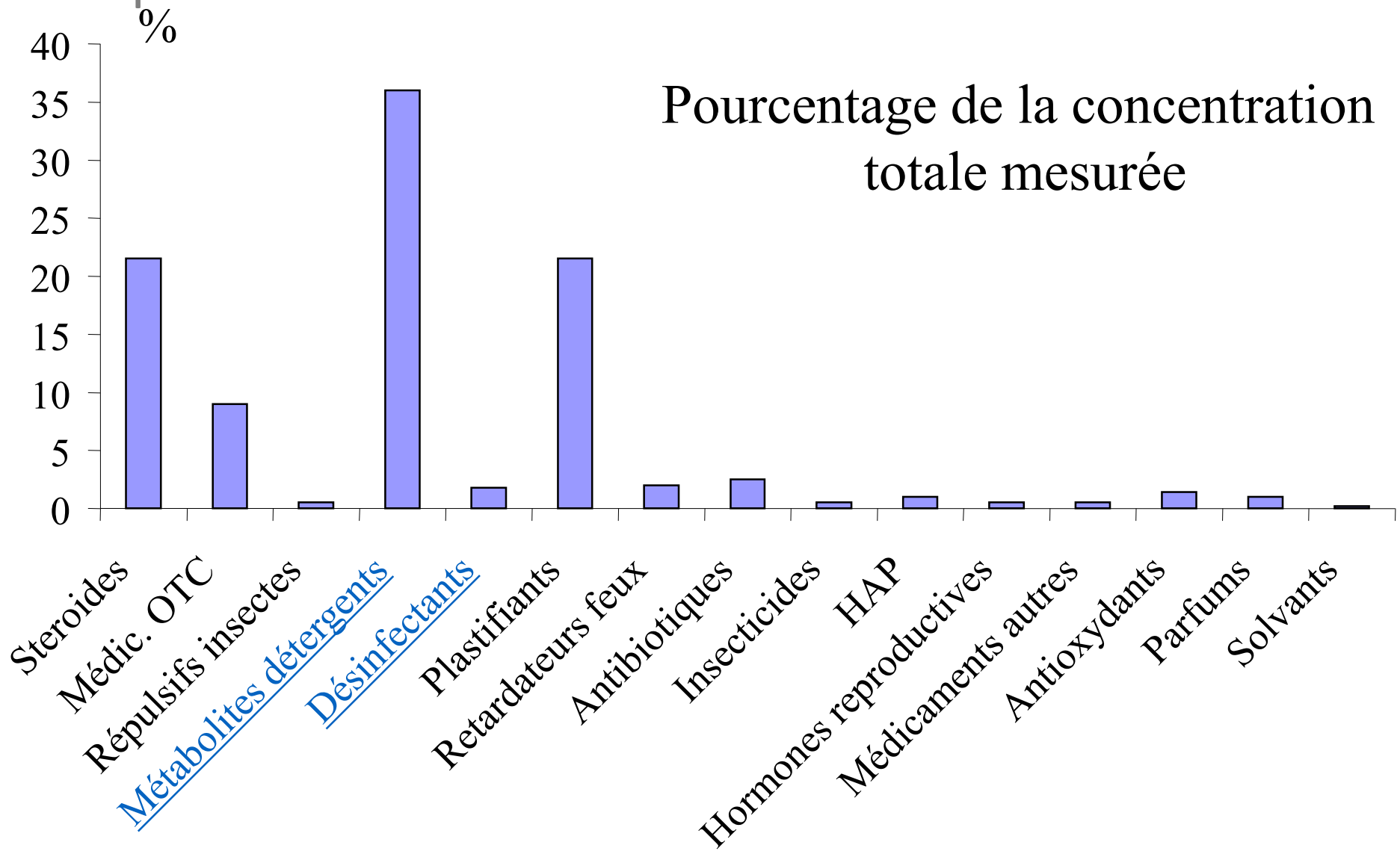
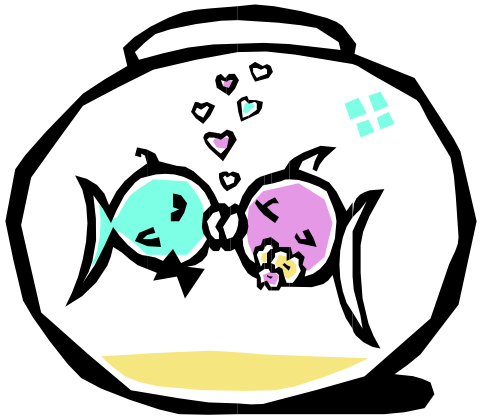


Micropollutants with Endocrine Disrupting Effects



UNE LISTE IMPRESSIONNANTE !

Alkylphénols (penta à nonyl)
Bisphénol A
2,4 dichlorophénol
Diethyhexyladipate
2,3,7,8 TCDD
2,3,7,8 Tetrachlorodibenzofuranne
Polychlorobiphényls
Octachlorostyrène
Hexachlorobenzène
Pentachlorophénol

Pesticides

2,4,5 T, 2,4 D, Alachlor, Aldicarb, Amitrole, Atrazine, Benomyl, β HCH, Carbaryl, Chlordane, Cypermethrine, DDT et métabolites, Dicofol, Dieldrine, Endosulfan, Ethylparathion, Lindane, Heptachlore, Heptachlore epoxyde, Kelthane, Kepone, Malathion, Mancozebe, Maneb, Methomyl, Mirex, Parathion, Permethrine, Pyrethroides de synthèse, Toxaphène, Zineb, Ziram.

Esters de phtalates

DEHP, BBP, DBP, DPP, DHP, DPrP, DCHP, DEP

Autres

Styrène (dimères et trimères)
Benzo(a) pyrène

Métaux lourds

Cadmium, Plomb, Mercure

Disinfectants and Endocrine Disruptors

- Quaternary ammoniums (benzalkonium chloride, …),
- Parabens (para-hydroxybenzoic acid esters, …),
- Halogenated phenols (hexachlorophene, o-phenyl phenol(PhP), …),
- Tri Butyl Tin,
- Triclosan,
- ???

TOXICITY (8)

HUMAN TOXICITY

The active substances are now better known for their toxicity and medical uses are more prudent (e.g. Hexachlorophene & talc Morhange in France !).

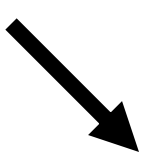
But the endocrine disruptor effects of some active biocides need to be better evaluated and we need to take into account the so-called « cocktail effect ».

This is certainly the actually less studied scientific question in relation with biocides.

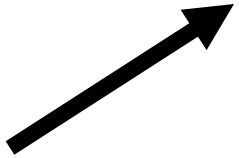
EFFETS COMBINES

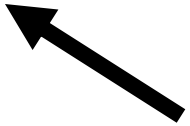
Augmentation de la clairance de la testosterone
- Endosulfan
- Mirex
- Chlordecone
- o, p' - DDT

Diminution de la synthèse de la testosterone
- Ketoconazole



Demasculinisation





Estrogénicité
- Endosulfan
- o,p' DDT
- Toxaphene
- Dieldrine
- Methoxychlore

Anti- androgénicité
- p,p'-DDE
- Vinclozine

Le Blanc *et al.* Mol. Cell. Endocrinol. (1997)

CONCLUSIONS

- Need of a better classification of disinfectants/antiseptics for human skin: biocidal products or/and medicinal products inside all Member States,
- Because of the possibility to induce resistant/tolerant subpopulations of microoraganisms, prudent and targeted use of both antibiotics and disinfectants at the efficient concentration,
- Need to study the endocrine disrupting effects of the disinfectants both for the wildlife and humans taking into account the potential cocktail effect.

THANK YOU FOR YOUR ATTENTION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POUR ENTRER DANS LE XXIe SIÈCLE...
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