

CURRENT SITUATION

➤ TESTING FOR SKIN SENSITISATION : INTEGRAL PART OF MOST "VERTICAL" **EU LEGISLATIONS REQUIREMENTS**

- Chemicals
- Biocides
- Plant protection products
- Cosmetics
- Pharmaceuticals
- Detergents
- Food additives

➤ SUBSTANCES MUST BE **SAFE** TO USE

→ ALTERNATIVE METHODS : SAME OR HIGHER LEVEL OF SAFETY

➤ USED FOR

- **HAZARD DETERMINATION**

- 1B
- CLASSIFICATION
 - LABELLING
- GHS (global harmonisation scheme), inc Cat 1A and 1B
- Critical to distinguish significantly sensitising substances from non-sensitising ones*

- **RISK ASSESSMENT** : RELATIVE POTENCY

*R43 : may cause sensitisation by skin contact

WHAT IS A "GOLD STANDARD" ?

IN DICTIONARIES :

Gold standard = Benchmark = point of reference - serving as a standard by which others may be measured or judged

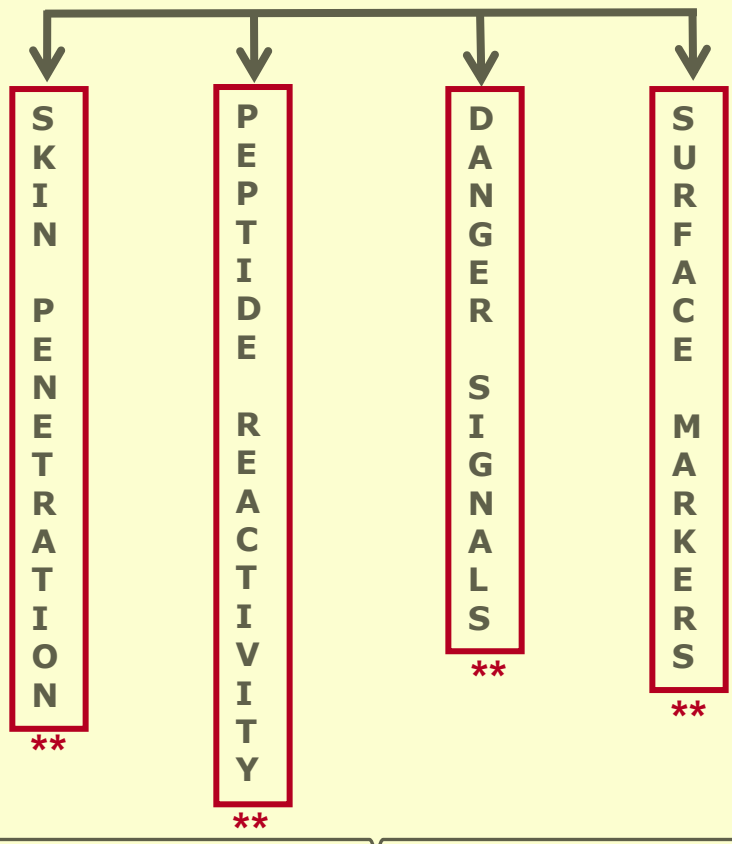
Gold standard = test/dataset with 100% sensitivity and 100% specificity..... **not realistic**

... Evaluated against definition ... should be **interpreted in the context of** history, physical findings and other test results ...

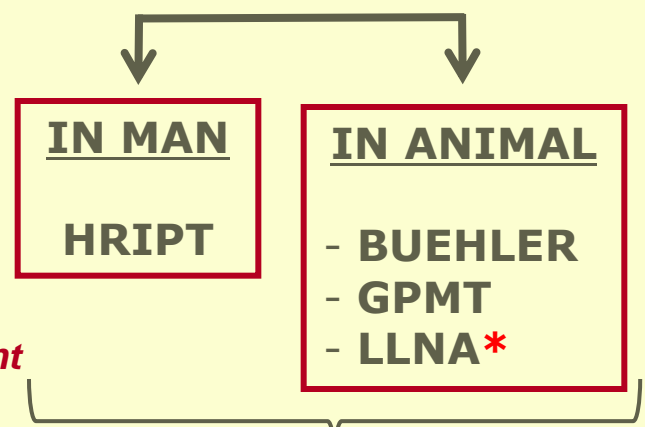
IS THERE A "GOLD STANDARD" ?

ACTUAL METHODOLOGY

IN VITRO TESTING



IN VIVO TESTING



* *Refinement Reduction*
 ** *Replacement*

INTACT IMMUNE SYSTEM

- HRIPT, Buehler, GPMT :
1 subjective read-out,
ethical issues
- LLNA :
1 objective read-out,
not for cosmetics after 2013

NON - INTACT IMMUNE SYSTEM KEY COMPONENT(S) OF IMMUNE REACTION

- 1 read-out : too simple
- > 1 read-out : battery → STRATEGY
- suitable for cosmetics

QUESTIONS

- AGAINST WHICH TEST OR DATA SET SHOULD NEW *IN VITRO* TESTS BE VALIDATED ? **THUS WHAT IS THE "GOLD STANDARD"?**

VALIDATION AGAINST :

THINK OF :

Structural data, chemical reactivity (irritancy), epidermal bioavailability (aqueous/lipidic systems), guinea-pig results, clinical data, experimental human data, presence of impurities, vehicle used, interfering substances (coloration), quality of test (positive control e.g. hexyl-cinnamic aldehyde, mercaptobenzothiazole) etc.

QUESTIONS

- AGAINST WHICH TEST OR DATA SET SHOULD NEW *IN VITRO* TESTS BE VALIDATED ? THUS WHAT IS THE "GOLD STANDARD"?

VALIDATION AGAINST :

- Human data ? Clinical evidence ?
 - GPMT data ?
 - LLNA data ?
- } considered as being equivalent (LLNA : first choice !)

- WHAT ARGUMENTS AND SCIENTIFIC DATA ARE AVAILABLE : PRO AND CONS TO USE AS THE GOLD STANDARD

- LLNA alone ?
- Open choice of LLNA / GPMT ?
- Weight of evidence approach ?
(data from all available sources advocated by GHS)

- FOR MANY CHEMICALS ONLY DATA FROM LLNA ARE AVAILABLE; WHAT IS THEN A WEIGHT OF EVIDENCE APPROACH ?

e.g. Are data such as SAR, general information on chemical class, on impurities, monomeric residue amounts sufficient ?