

SURFACTANT TOXICOLOGY

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Toxicology, Europe/Africa

Pilliod v. Monsanto

EX. 0075

Case No: RG17862702

SURFACTANT TOXICOLOGY

Outline

- *Toxicity related to surfactant action*
- *Specific cases of toxicity*
 - *Genotoxicity*
 - *Oestrogenicity*

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Toxicity related to surfactant action

| | |
|-------------------|--|
| Skin | <ul style="list-style-type: none">• Corrosion (tissue destruction)• Irritation (inflammation)• Sensitisation (allergy)• Irritative dermatitis |
| Eyes | <ul style="list-style-type: none">• Corrosion (tissue destruction)• Irreversible corneal lesions (blindness)• Irritation (inflammation eye lids) |
| Intestines | <ul style="list-style-type: none">• Necrosis• Inflammation• Water retention → hypovolemic shock |
| Kinetics | <ul style="list-style-type: none">• Poor skin absorption• Poor intestinal absorption• Enhancement of skin absorption of other chemicals |

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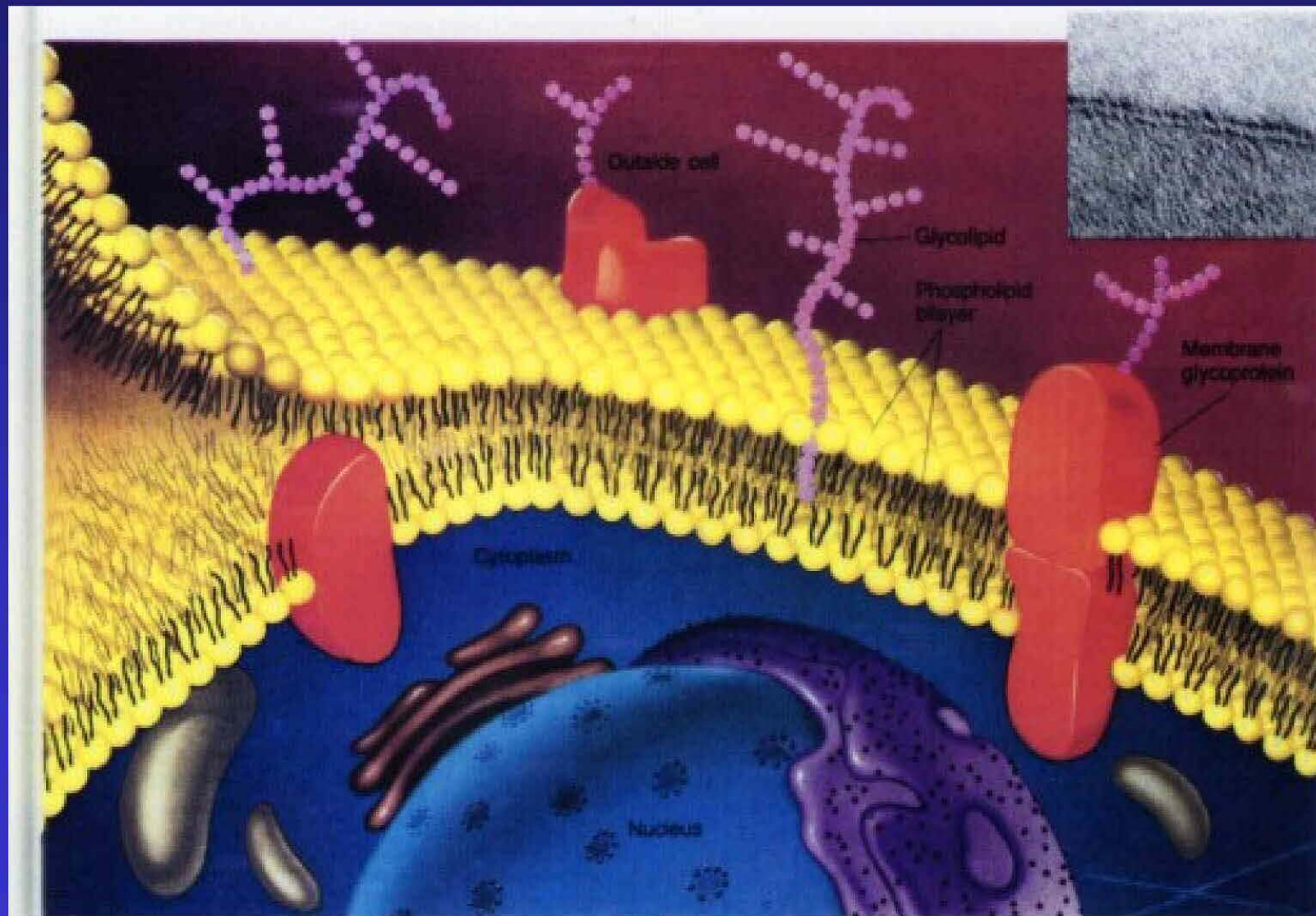
Toxicity related to surfactant action

Common toxicologic mechanism:

Disturbance of cell membrane integrity

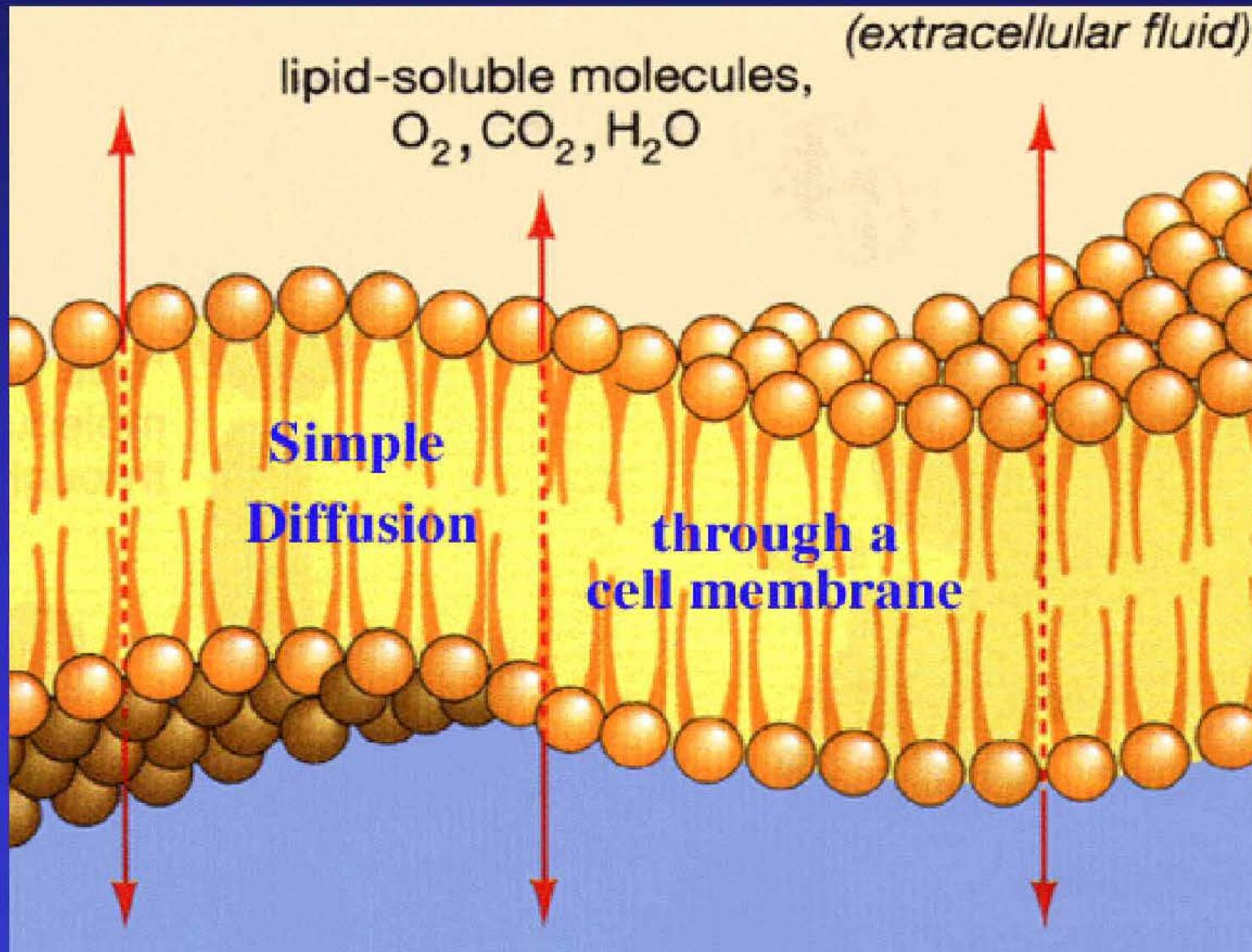
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Toxicity related to surfactant action



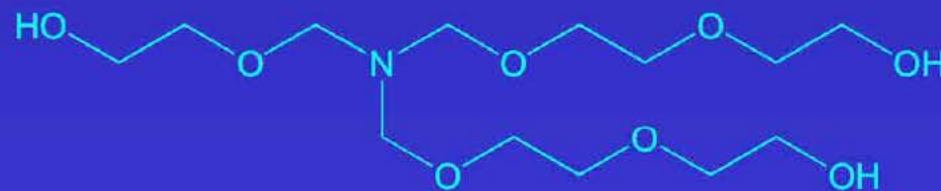
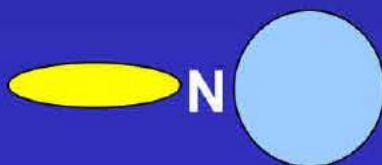
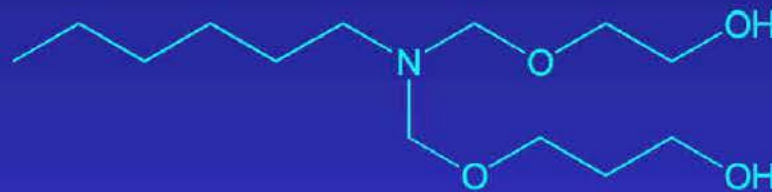
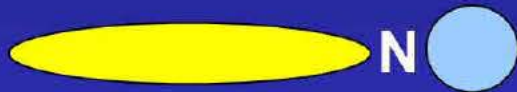
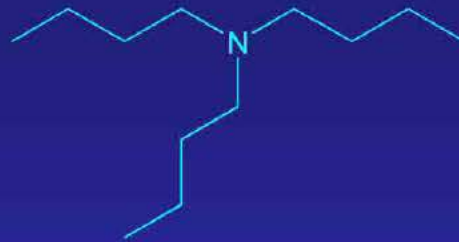
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Toxicity related to surfactant action



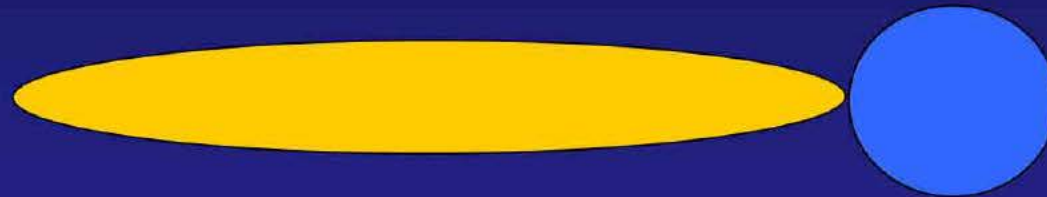
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Poly-ethoxylated fatty amines



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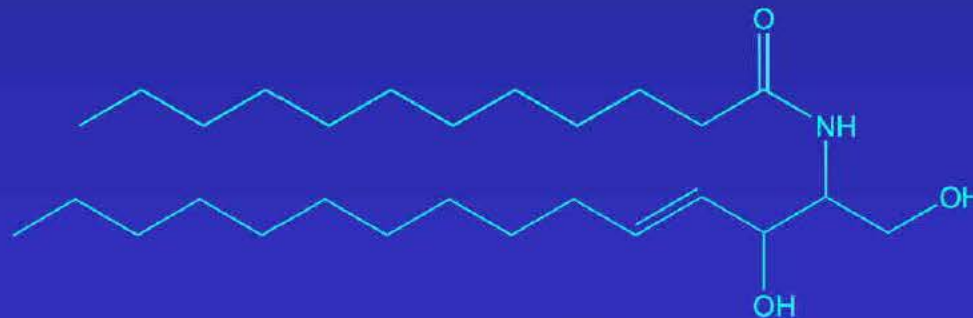
Sphingolipids of the cell membrane



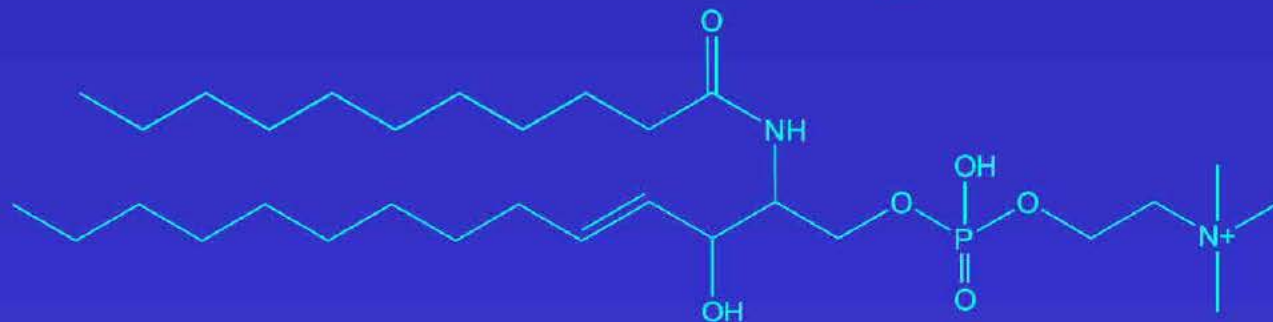
Sphingosine



Ceramide

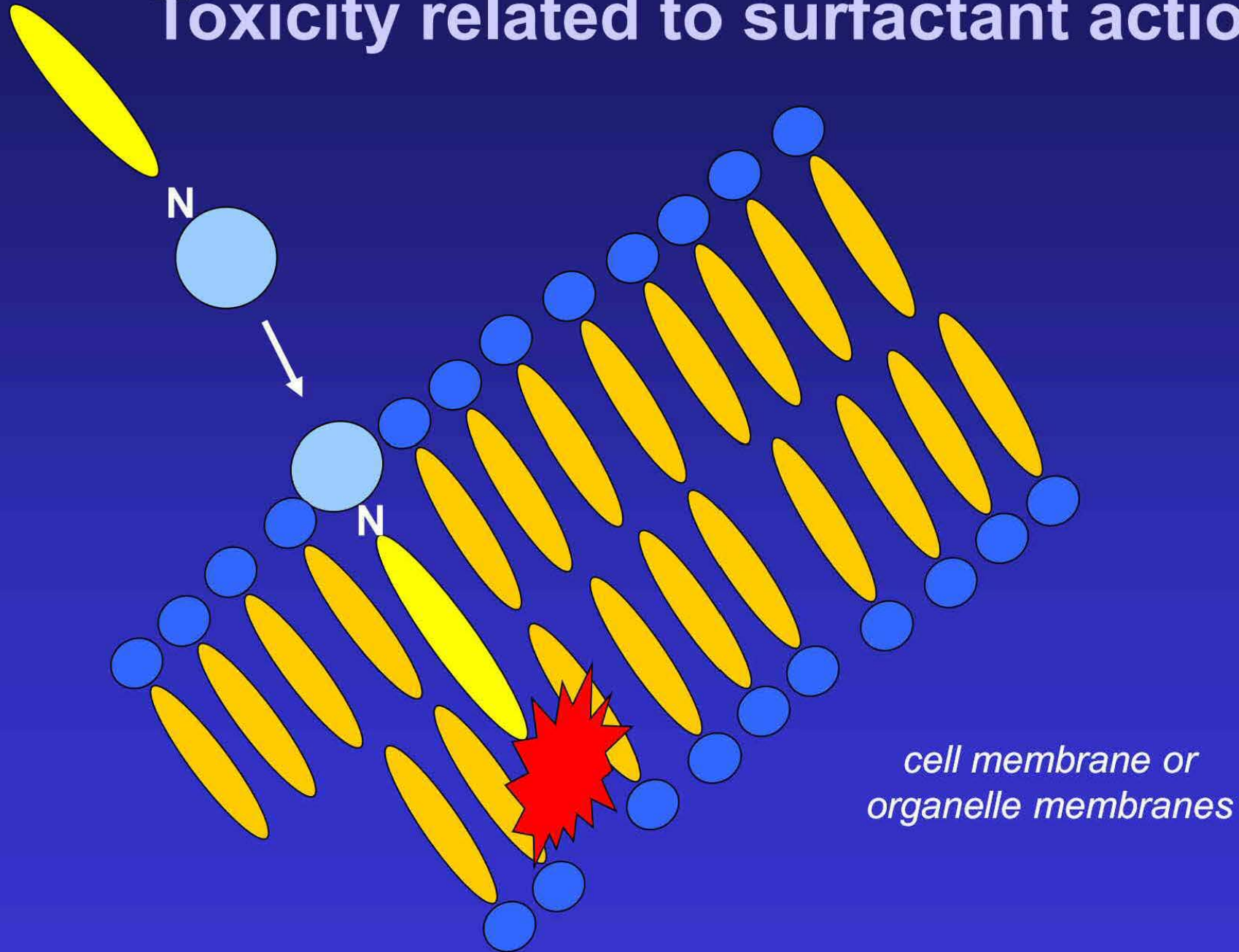


Sphingomyelin



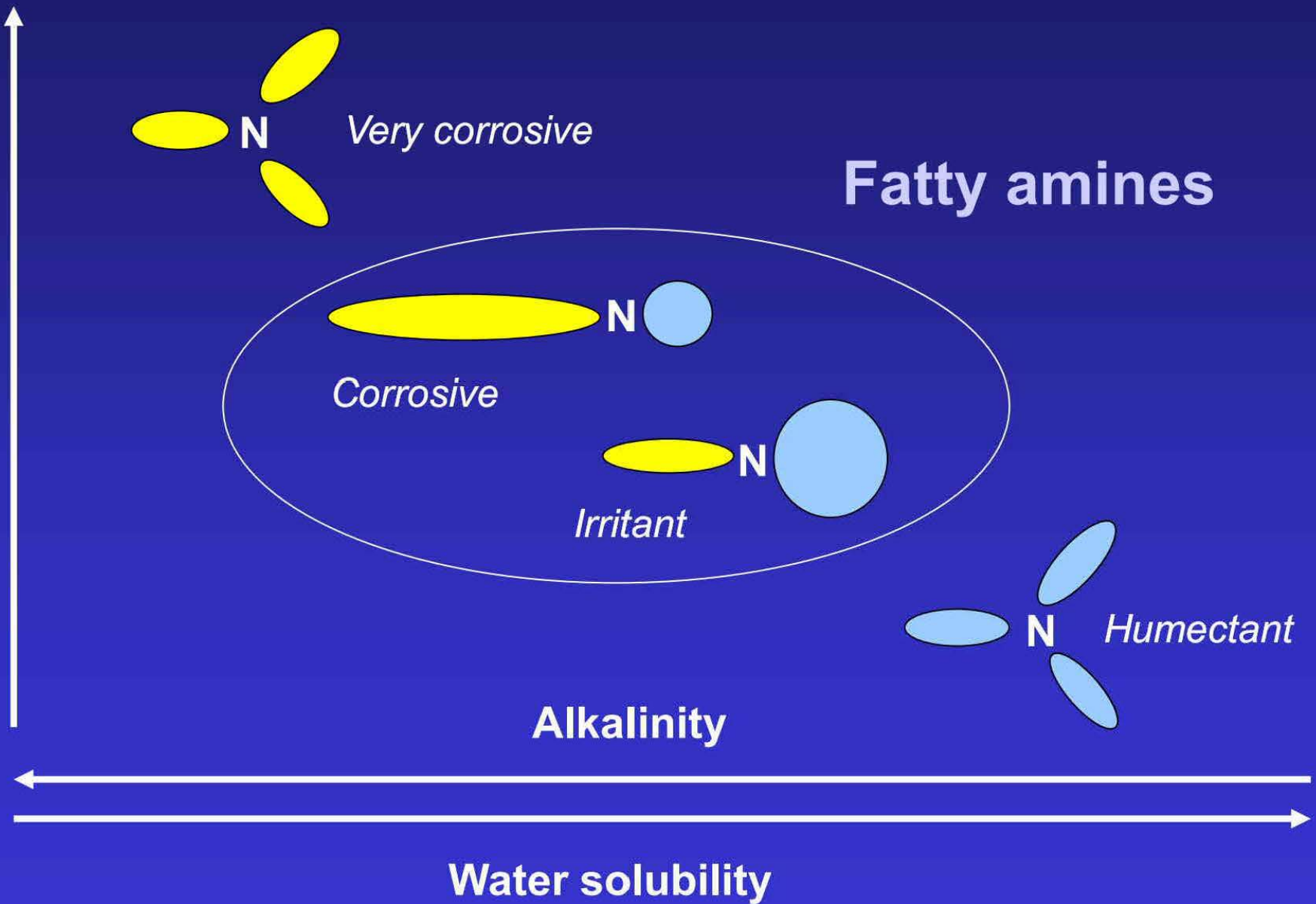
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Toxicity related to surfactant action



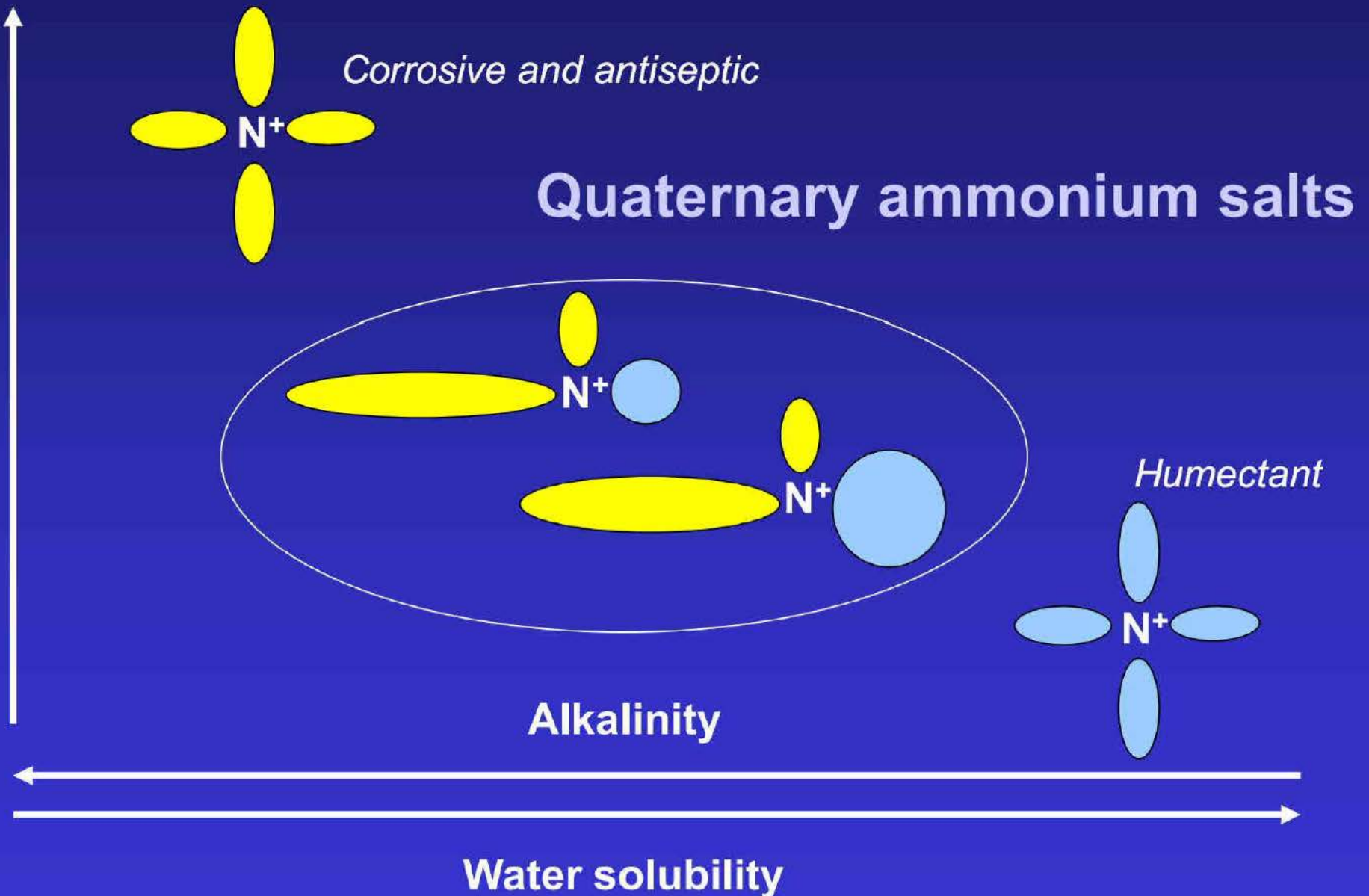
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Aggressivity to mucous membranes/skin

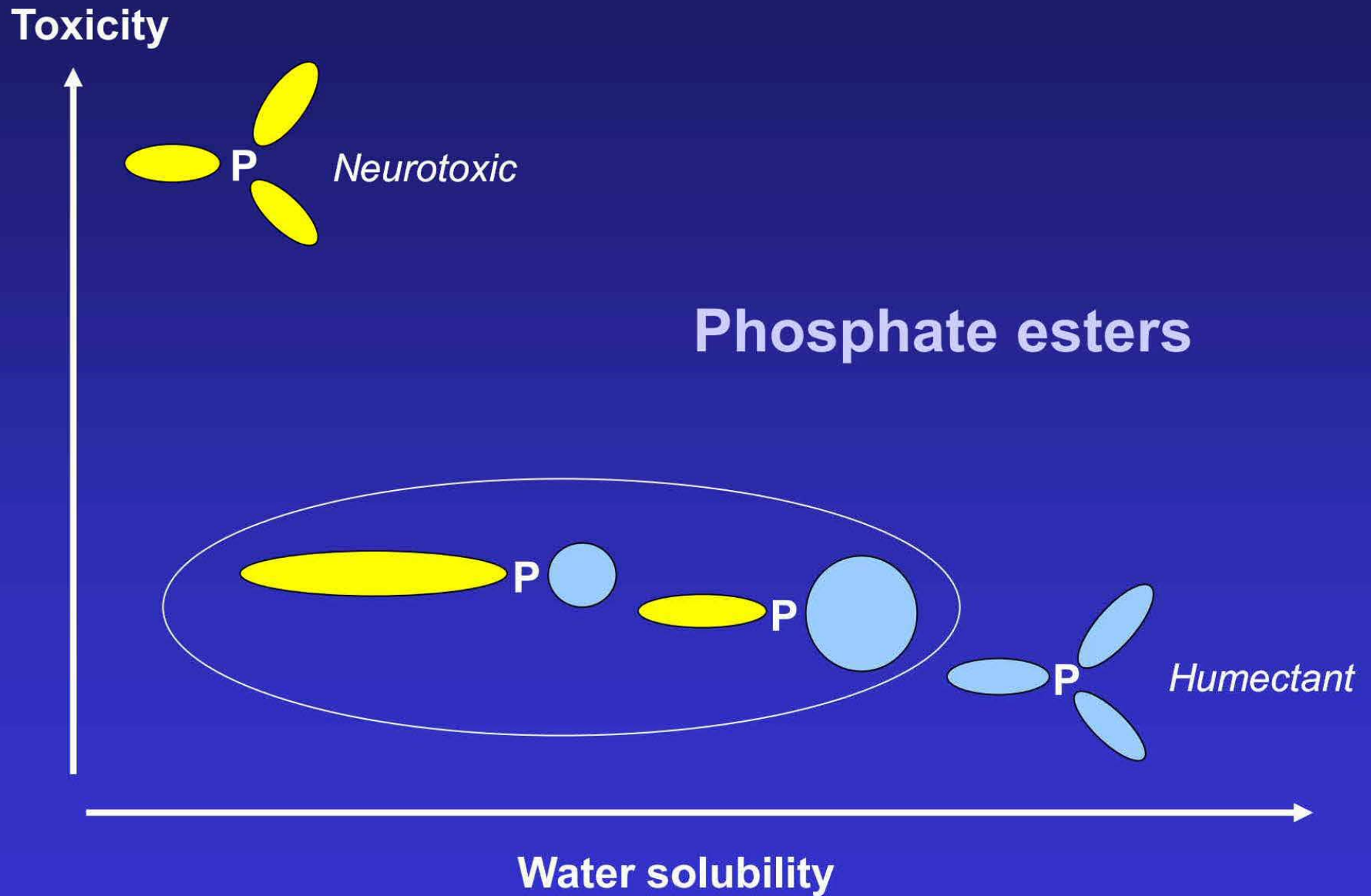


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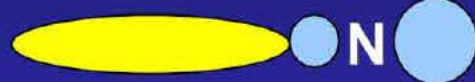
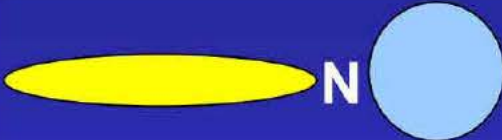
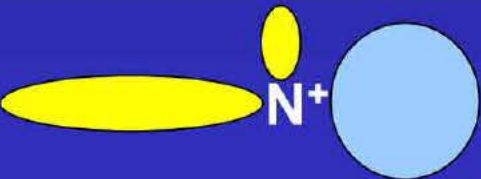
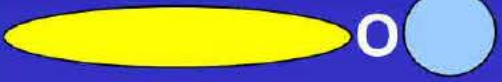
Aggressivity to mucous membranes/skin



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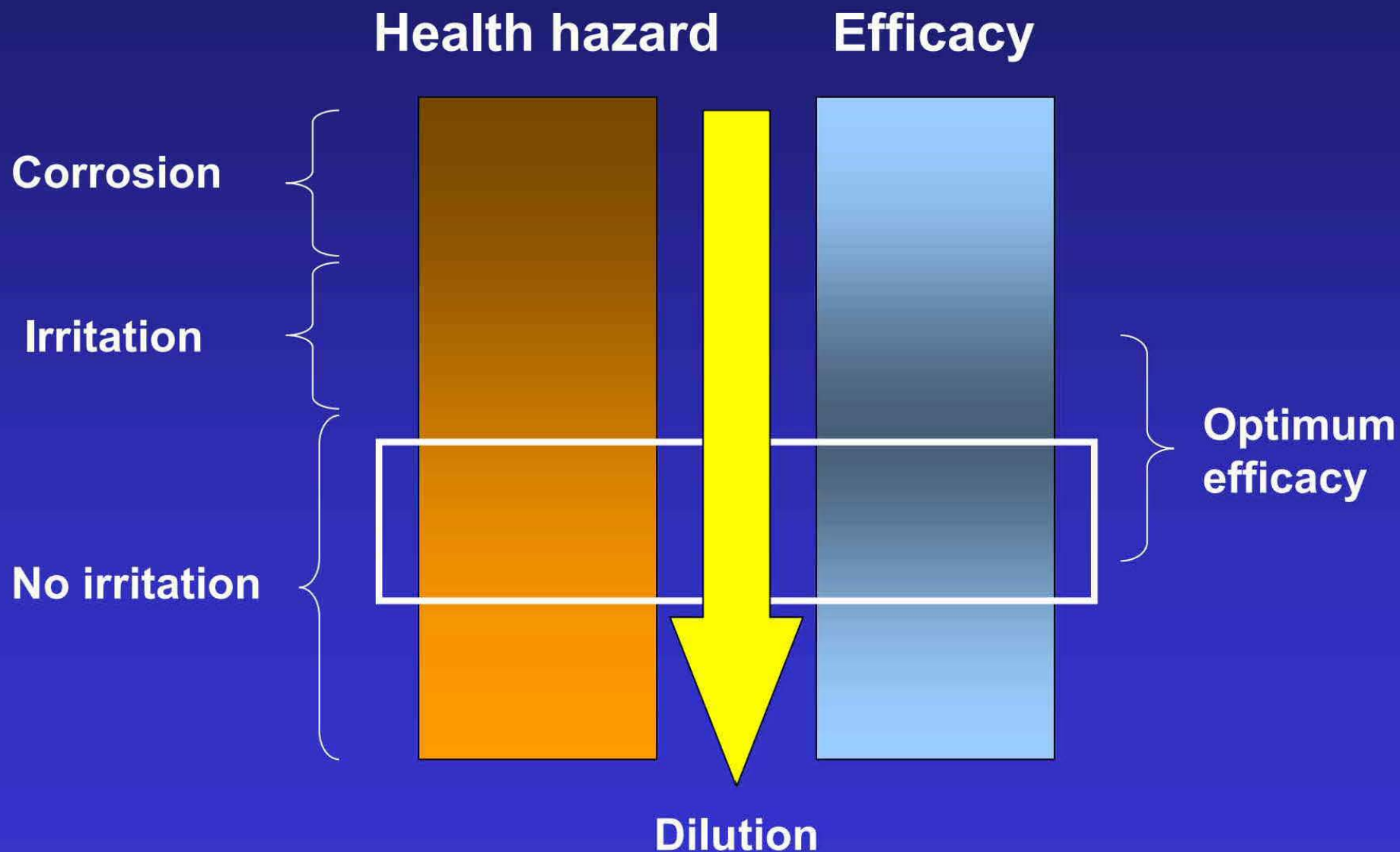


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| Surfact. | Type | Cyto- toxicity (EC50, ug/mL) | Eye irritation (EU class) | Fish toxicity (LC50, mg/L) |
|-----------------|---|---------------------------------------|---------------------------------|-------------------------------------|
| HOE T 3329 |  | 28 | Xi, R41 | 0.1-1 |
| MON 0818 |  | 26 | Xi, R41 | 1.3 |
| Dodigen 4022 |  | 233 | < Xi | > 500 |
| Tween 20 |  | 695 | 0 | 216 |
| G3 mix | Dodigen 4022 + Tween 20 | 2068 | < Xi | 500-1000 |

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Toxicity related to surfactant action

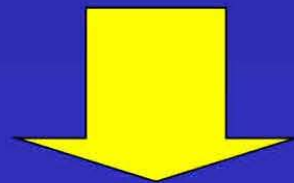


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Specific toxicity cases: DNA adducts

Peluso et al., 1998:

Increase of DNA adducts in liver and kidneys of mice after intraperitoneal injection (i.p.) of Italian Roundup (MON 35050, not anymore commercial) dissolved in DMSO/olive oil



This in-vivo genotoxicity finding was cause of concern to regulatory authorities

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Specific toxicity cases: DNA adducts

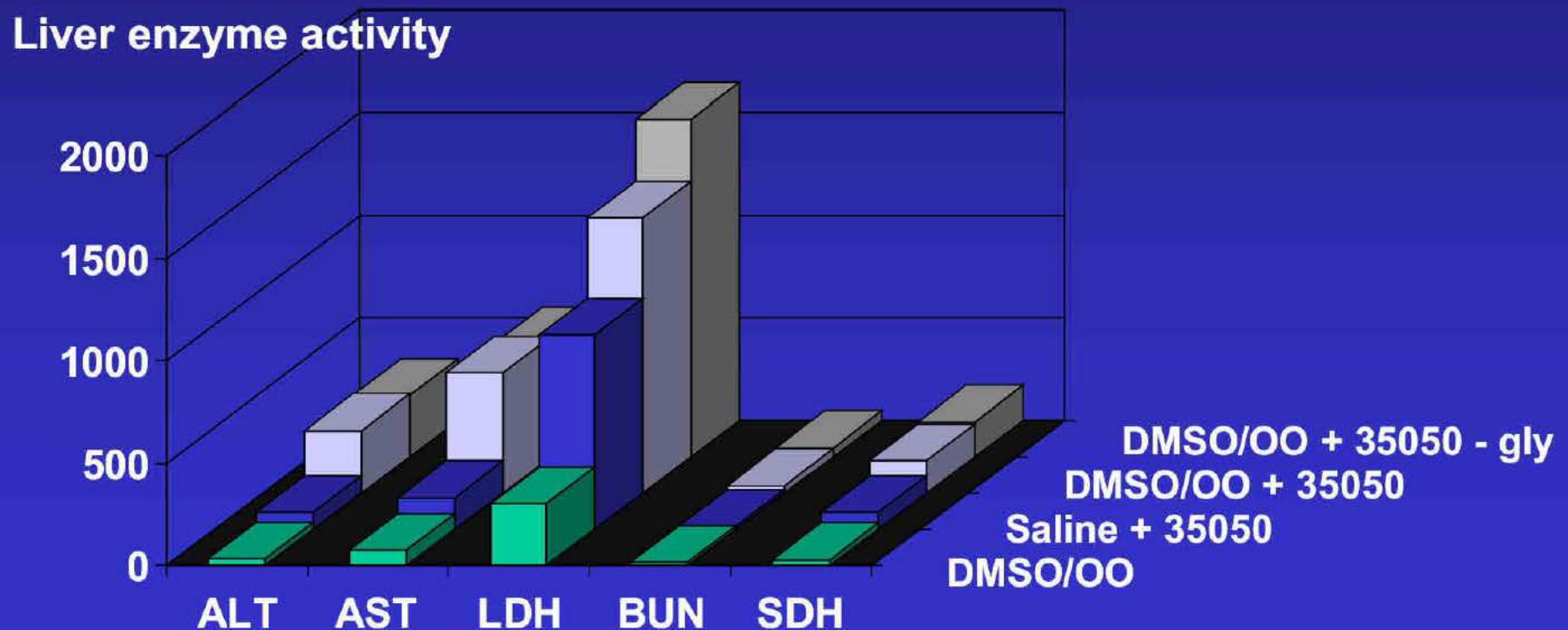
To better understand the significance of these findings Monsanto undertook research to examine the role of:

- *The route of administration (i.p. vs oral)*
- *The vehicle (DMSO/olive oil vs saline)*
- *The surfactant (MON 35050 with and without glyphosate)*

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Specific toxicity cases: DNA adducts

Liver toxicity in the CD-1 mouse:
influence of surfactant and vehicle after I.P. administration

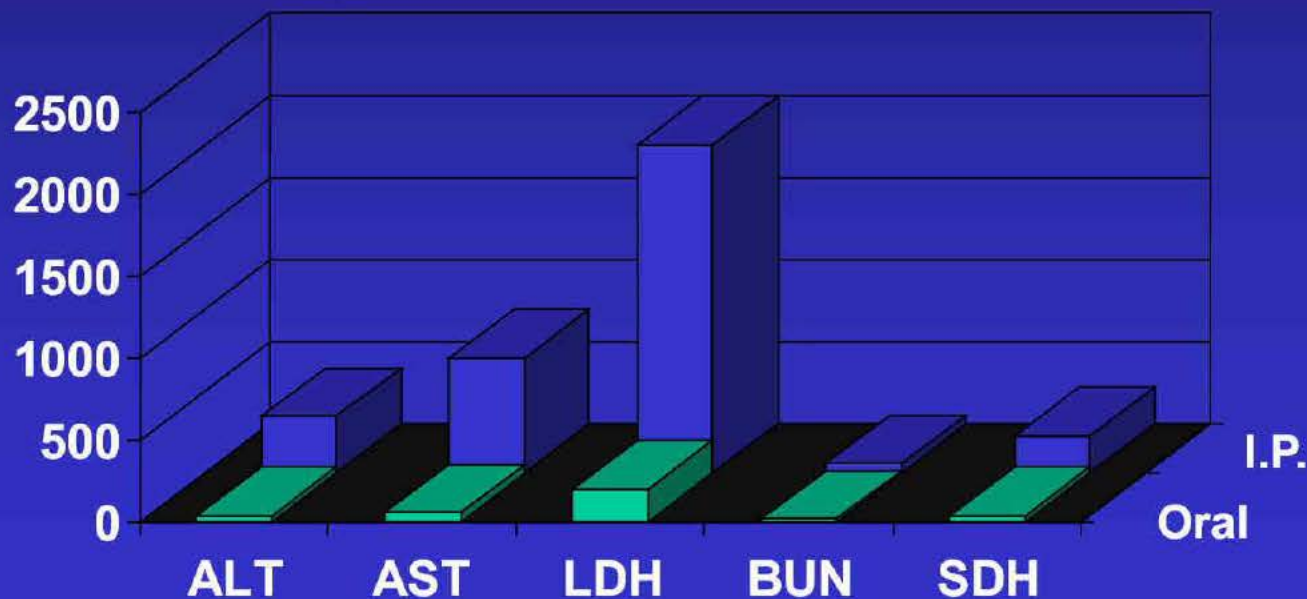


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Specific toxicity cases: DNA adducts

Liver toxicity in the CD-1 mouse:
influence of route of administration

Liver enzyme activity

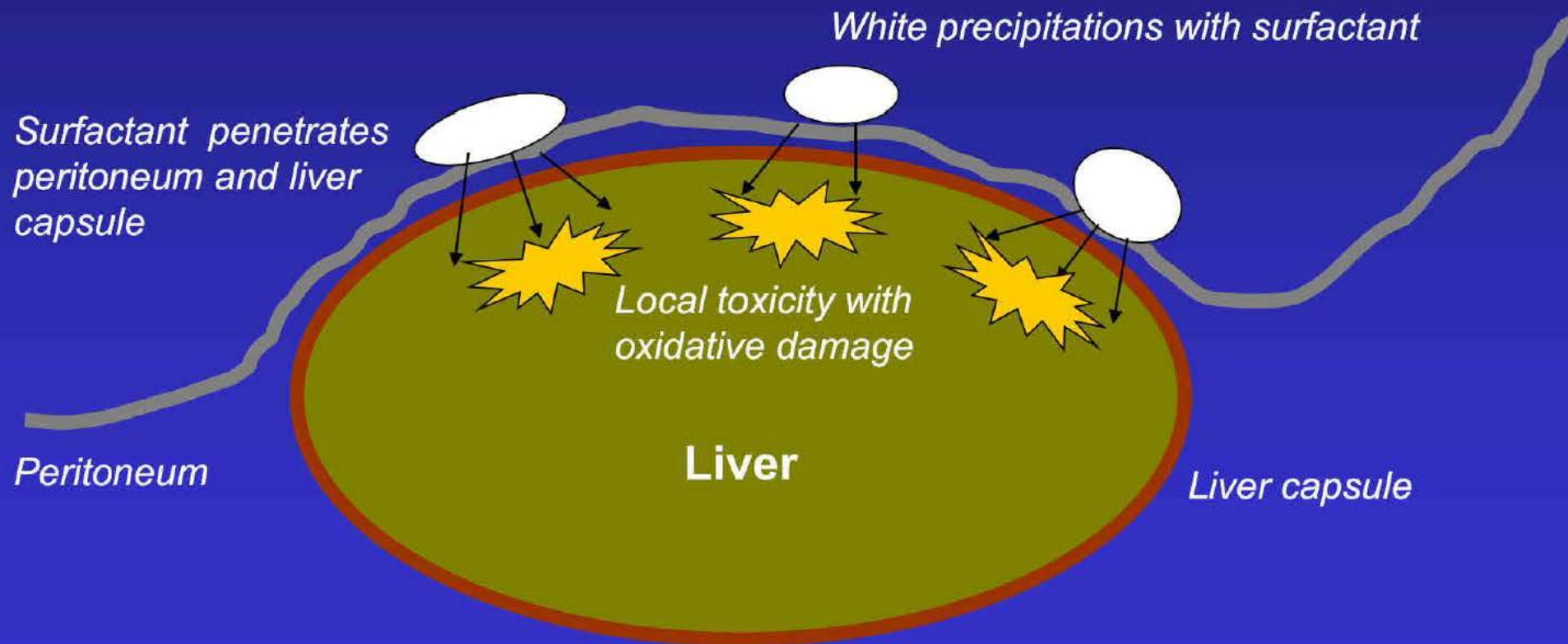


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Specific toxicity cases: DNA adducts

Mechanism

Peritoneal cavity



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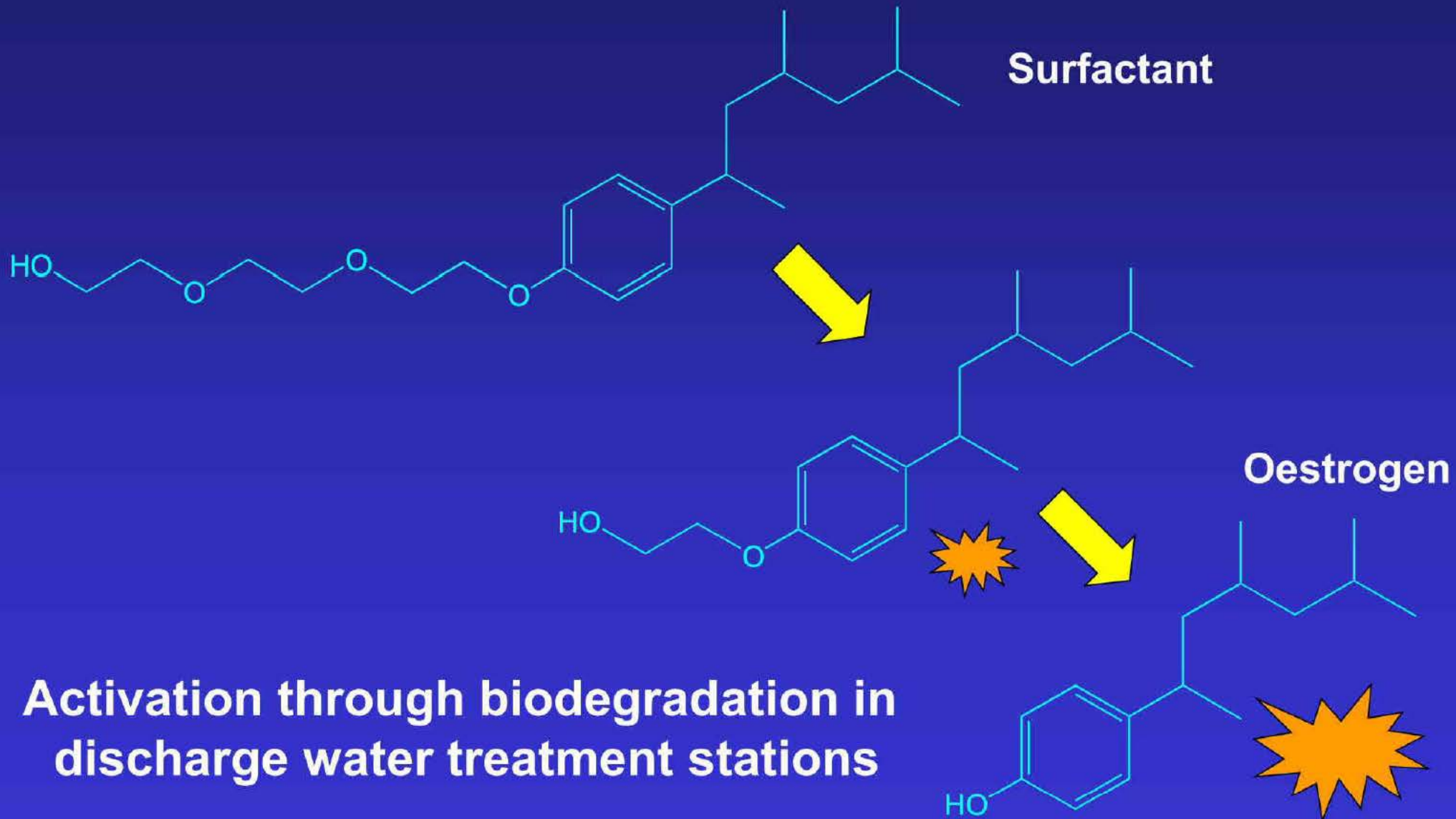
Specific toxicity cases: DNA adducts

Conclusions of MON 35050 case

- *The I.P. route is an inappropriate route of administration*
- *The vehicle (DMSO/olive oil) produces precipitates onto the peritoneal membrane with very high local concentrations of surfactant as a consequence → inflammation in underlying organs!*
- *The surfactant (alkyl sulphate) is the cause of the oxidative damage of DNA in liver and kidneys and not glyphosate*
- *The observation of the EU/BBA on the Peluso et al. paper was: “...some indications of DNA damage have been observed...rather due to cytotoxic properties of the formulation ...”*

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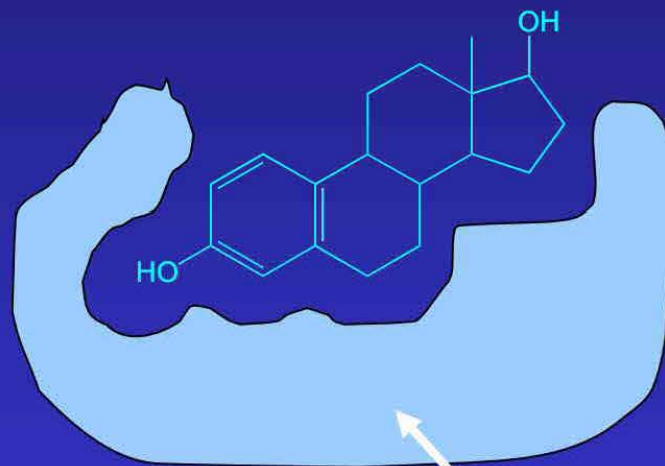
Specific toxicity cases: Oestrogenicity



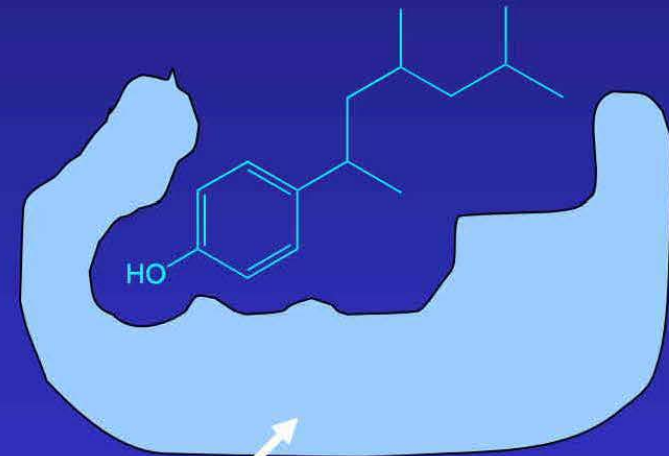
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Specific toxicity cases: Oestrogenicity

17 β -oestradiol



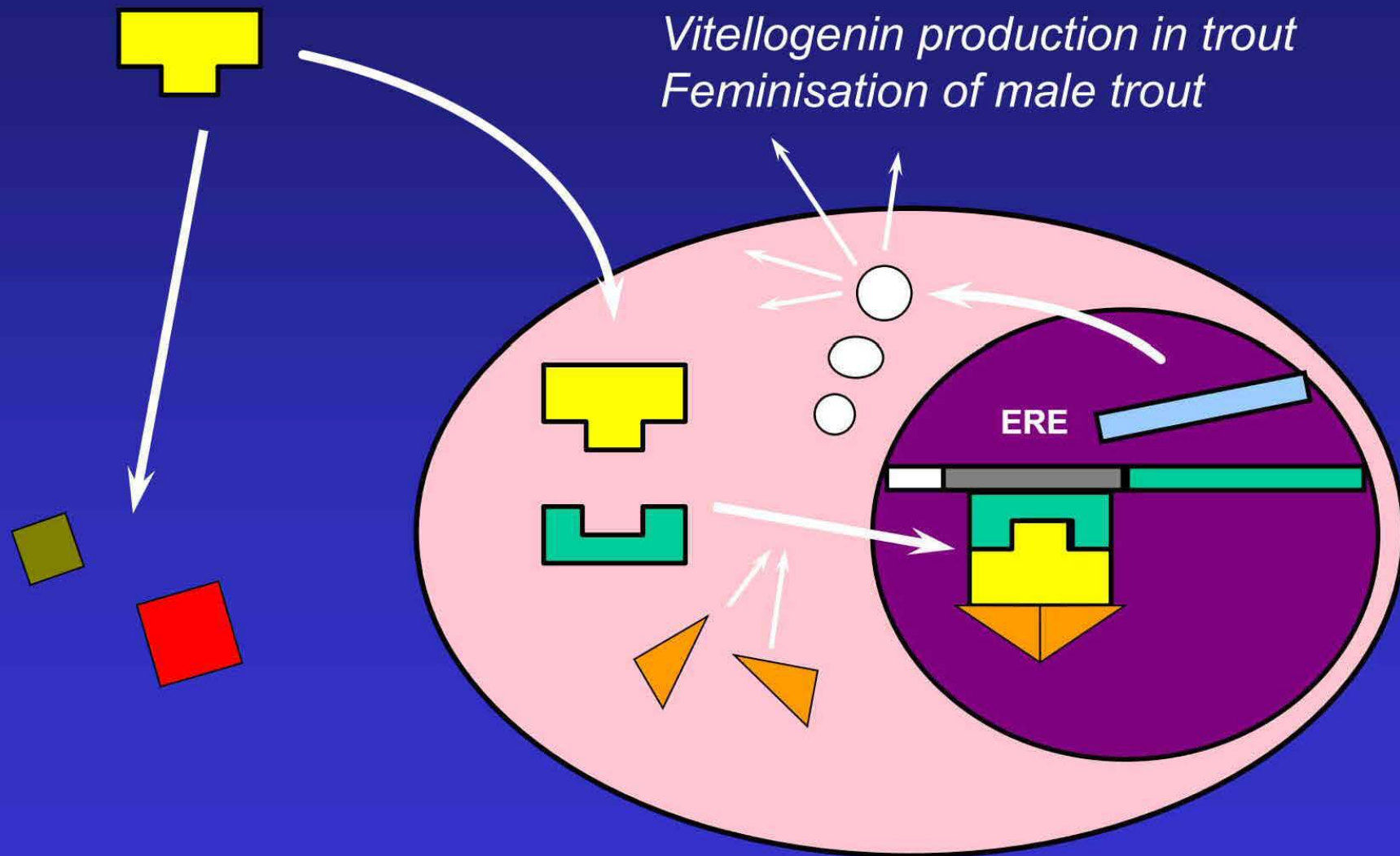
4-nonyl phenol



Oestrogen receptor

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Specific toxicity cases: Oestrogenicity



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Specific toxicity cases: Oestrogenicity

| | In-vitro | | | In-vivo | | |
|-----|-----------------|-----------|-------------|----------|--------------|----------------------|
| | Recept. binding | Prolifer. | Transcript. | Uterotr. | Hershberger | Reprotox. 2-gen |
| BBP | ER | ER | ER | | Peripubertal | |
| DBP | ER | ER | ER | | | Sem. Ves. Penis (F1) |
| NP | ER | ER | ER | | | Vaginal opening |
| BPA | ER | ER | ER | | Peripubertal | |

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Specific toxicity cases: Oestrogenicity

Conclusions of the case the polyethoxylated nonyl phenol surfactants (1)

- *Polyethoxylated nonyl phenol (and octyl phenol, decyl phenol, undecyl phenol, dodecyl phenol) surfactants biodegrade to form oestrogenic chemicals (mimic female hormones).*
- *Nonyl phenol has been shown to be oestrogenic in mammals in-vitro and in-vivo, however, the potency is approx 1,000-10,000 times lower than that of natural oestradiol.*
- *Nonyl phenol has been shown in-vitro, in vivo and in the field that it can feminise fish at environmentally relevant concentrations*

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Specific toxicity cases: Oestrogenicity

Conclusions of the case the polyethoxylated nonyl phenol surfactants (2)

- *An effort will have to be done by the pesticide industry to avoid using these surfactants in new formulations and whenever practically possible to replace them in existing formulations*
- *Monsanto Europe successfully undertook research to find a suitable replacement for polyethoxylated nonyl phenols. The new surfactant mix has similar technical properties and does not biodegrade into oestrogenic molecular species. It has already been proposed to replace surfactants in triallate formulations.*

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General conclusions

- *Surfactants are biologically not “inert”, they can be toxic and this must be addressed*
- *Part of the toxicity of surfactants is related to the surfactant action which destabilises cell membranes*
- *Part of the toxicity of surfactants can be specific (skin sensitisation, oestrogenicity)*
- *The toxicity of surfactants depends of their concentration in the formulation*
- *The high added value of herbicide formulations containing surfactants resides in the optimal compromise between efficacy and safety for man and the environment*