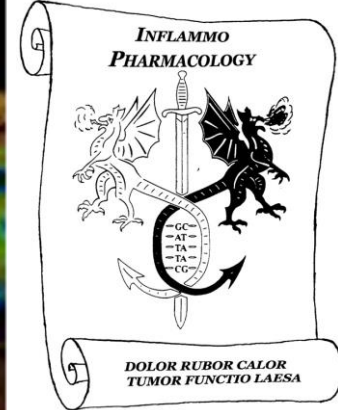


# Festschrift: Late Barrie Vernon-Roberts & those working on Pharmacotherapy of Inflammatory Diseases

Friday 5 July 2019

## Looking, Feeling and Modelling from the Outside In



The Institute

basil hetzel institute for translational health research

# Michael Roberts



School of Pharmacy & Medical Sciences,  
University of South Australia, Adelaide  
& Diamantina Institute, University of  
Queensland, Brisbane  
AUSTRALIA



TRANSLATIONAL RESEARCH INSTITUTE

AUSTRALIA



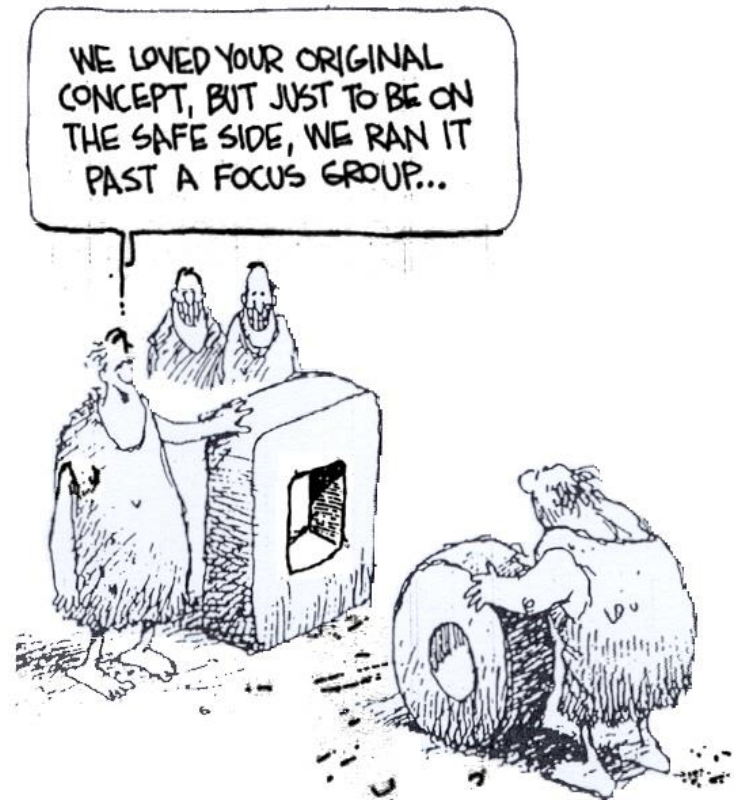
THE UNIVERSITY  
OF QUEENSLAND  
AUSTRALIA

DIAMANTINA  
INSTITUTE

# Consumer therapeutics and safety : from the outside looking in - scope

- Why the passion for pharmacotherapeutics for inflammation and its sequelae?
- Aspirin & salicylates
- Topical anti-inflammatories
- Sunscreen safety, i.e. safe prevention of sun induced skin inflammation
- ***And, along the way, I will give some reflections!***

*Successful innovation may require you to believe in yourself against the advice of your many colleagues!*



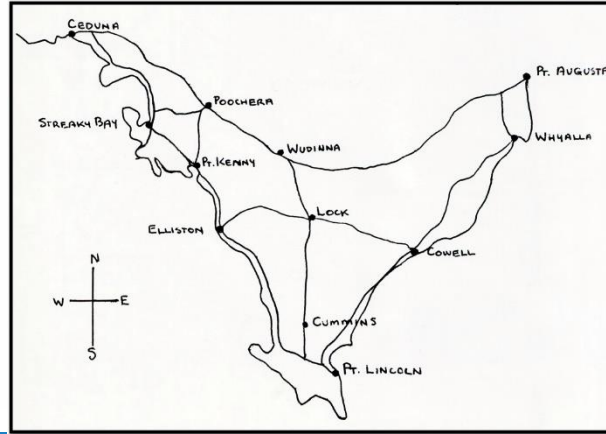


# Life is a journey and not a destination

Lynn H. Hough 1920

Journey for a child on a farm

- ❖ Defined my later choice for a career in medical research
- ❖ Assisted by my passion for maths, physics & chemistry
- ❖ Crucial survival & creative skills
- ❖ Isolation = limited social skills?



Vistas from Elliston & Dutton Bay – our holiday venues



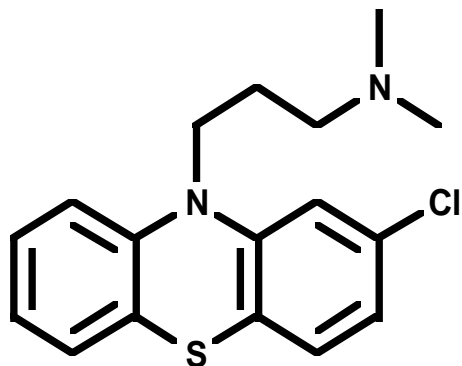
1966 rheumatoid arthritis cripple



# Key clinical experience as an intern that influenced my passion for & direction in research!

## Clinical case:

Older patient with intractable hiccups!



**Chlorpromazine [Largactil®]**

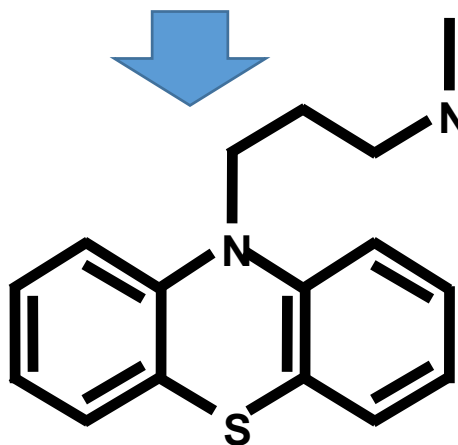


Old RAH as intern clinical pharmacy



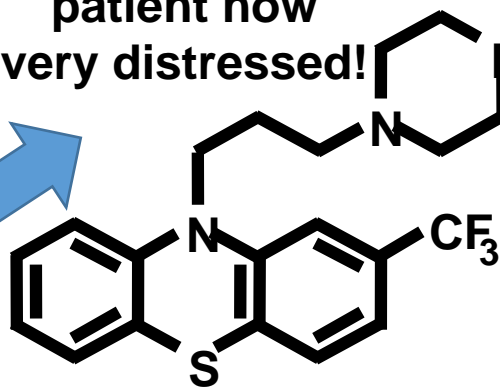
*In those days, the geriatric ward was not a focus for clinical pharmacy*

Allergic reaction!



**Promethazine [Phenergan®]**

Made it worse - patient now very distressed!



**Trifluoperazine [Stelazine®]**

But why was this ward getting “buckets of Betnovate® cream” when it is so expensive?

Key source of passions for:

- Therapeutics in elderly
- Drug chemical structure – activity relationships
- Topical delivery
- Adverse reactions/toxicity
- Cost - effectiveness

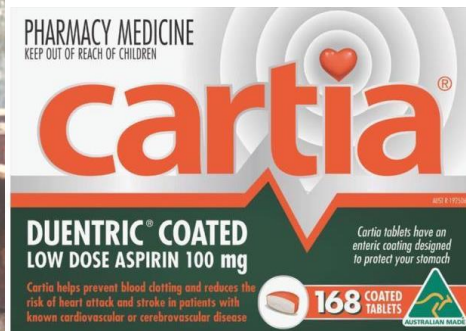
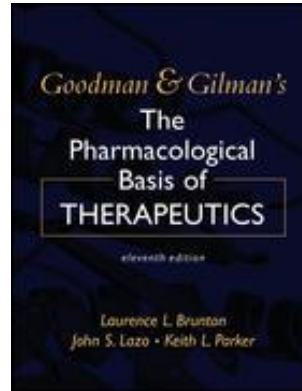


# Aspirin, a fantastic drug that, along with its salicylate metabolite, brings us all together

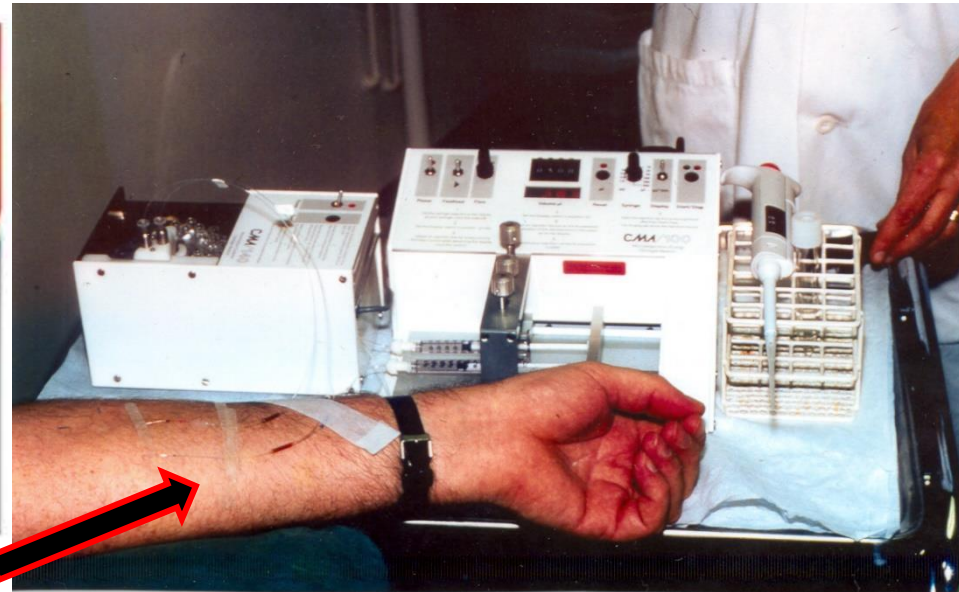
- My first human work explored the bioequivalence of enteric coated sodium salicylate products in 1973
- Pharmacokinetic studies in rheumatoid arthritis, liver disease patients & the elderly in Tasmania & Flinders with Peter Brooks
- Also profound was work on aspirin's anti-platelet adverse effect with Lyndsay McLeod & Janet Vial (*Lancet* 1: 1153, 1986).
- And it is about generations - Ric, Garry and Felix key mentors to my eldest son



Dr Bill Flux & Sue Owen in field

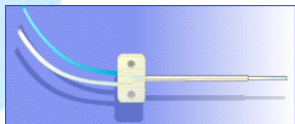
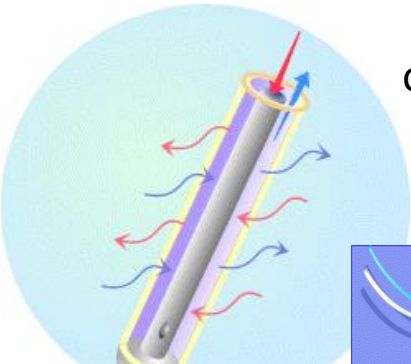
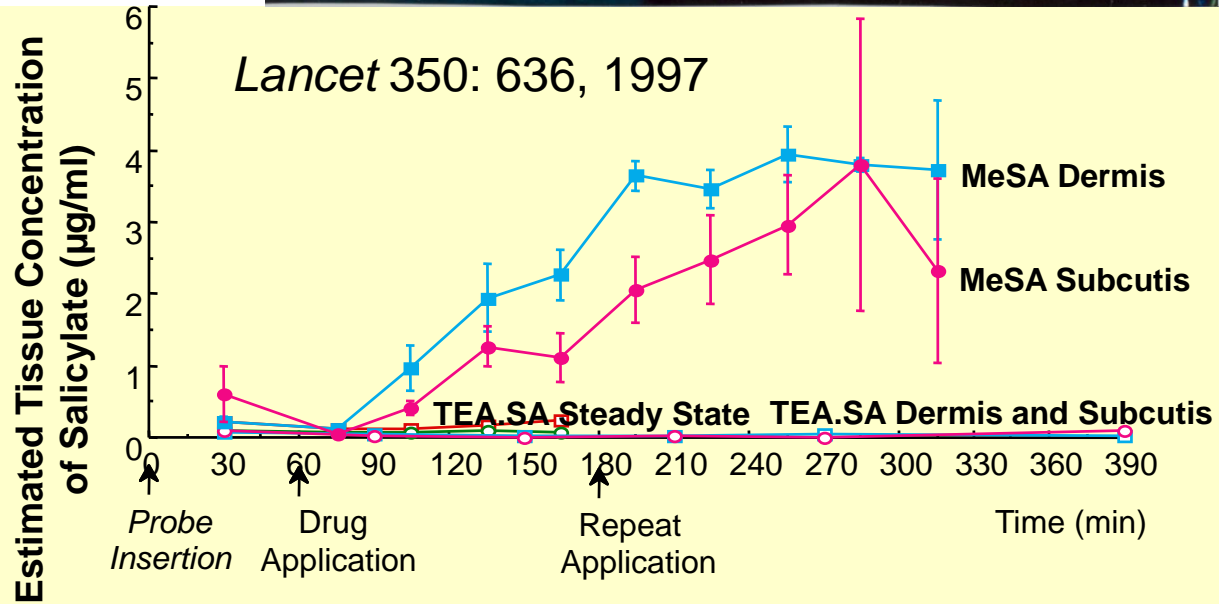


# Could one treat pain & inflammatory conditions topically to avoid systemic adverse effects?

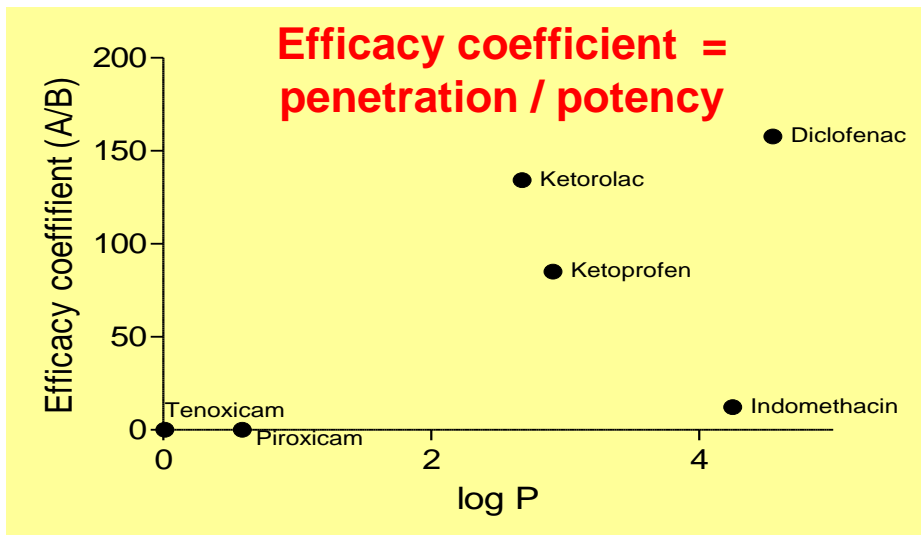
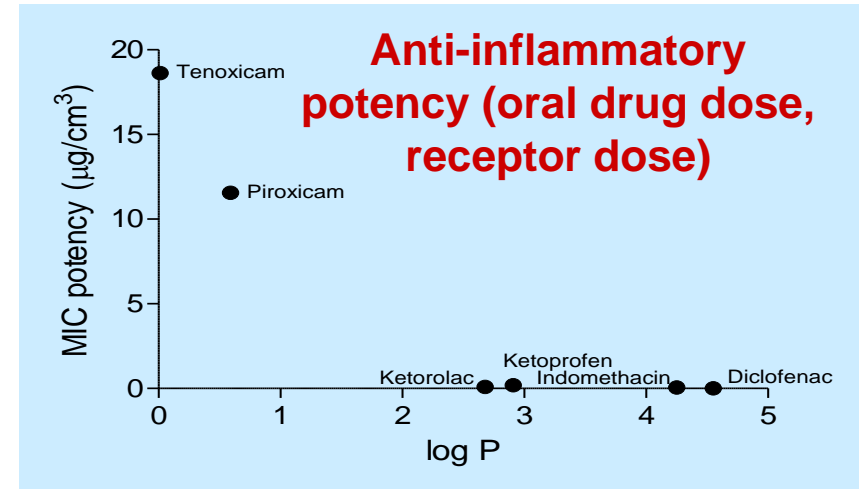
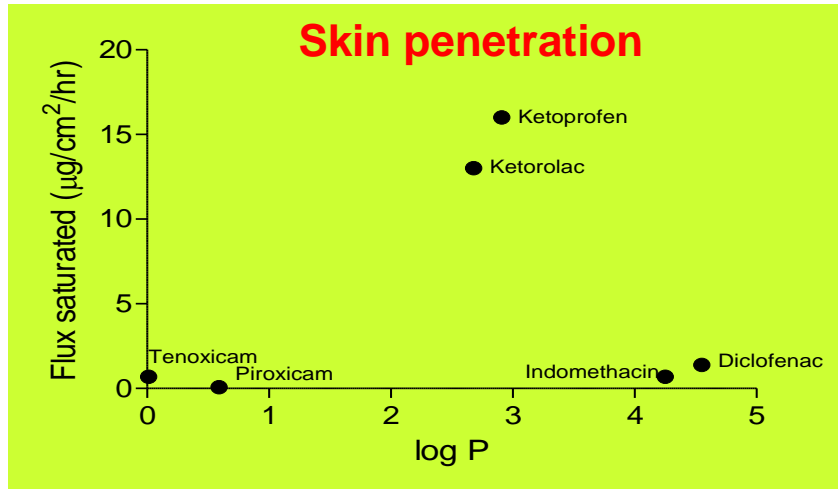


## Microdialysis probes

Chris Anderson, expat, Professor of Dermatology, University of Linköping, Sweden



# Which NSAID for topical use?



- Diclofenac is stand out NSAID
- Ketoprofen not bad
- Need data for ibuprofen

*Jepps et al Adv Drug Del Rev 65 (2013) 152–168*



# Topical administration of other diclofenac for osteoarthritis & other conditions

## Advantageous over systemic delivery?

- Avoid systemic delivery and filling up whole body.
- Critical for certain drugs, e.g. newer oral anticoagulant drugs
- How deep?
- Placebo effect?

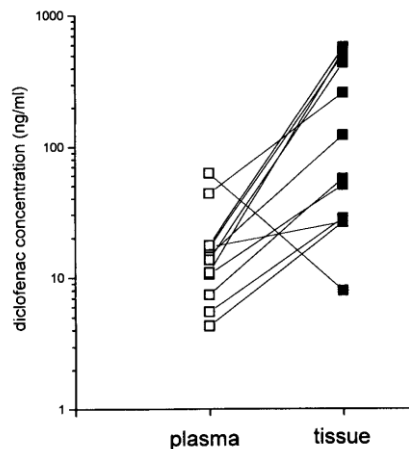
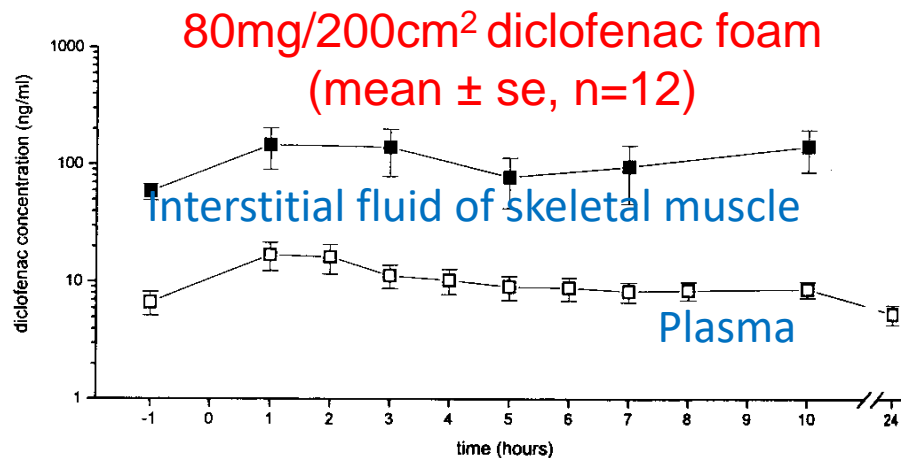
Efficacy can be tricky to quantify:

40+% soft tissue and joint disorders respond to placebo

*NSAIDs give 60-80% response*

## Microdialysis after repeated topical dosing of diclofenac

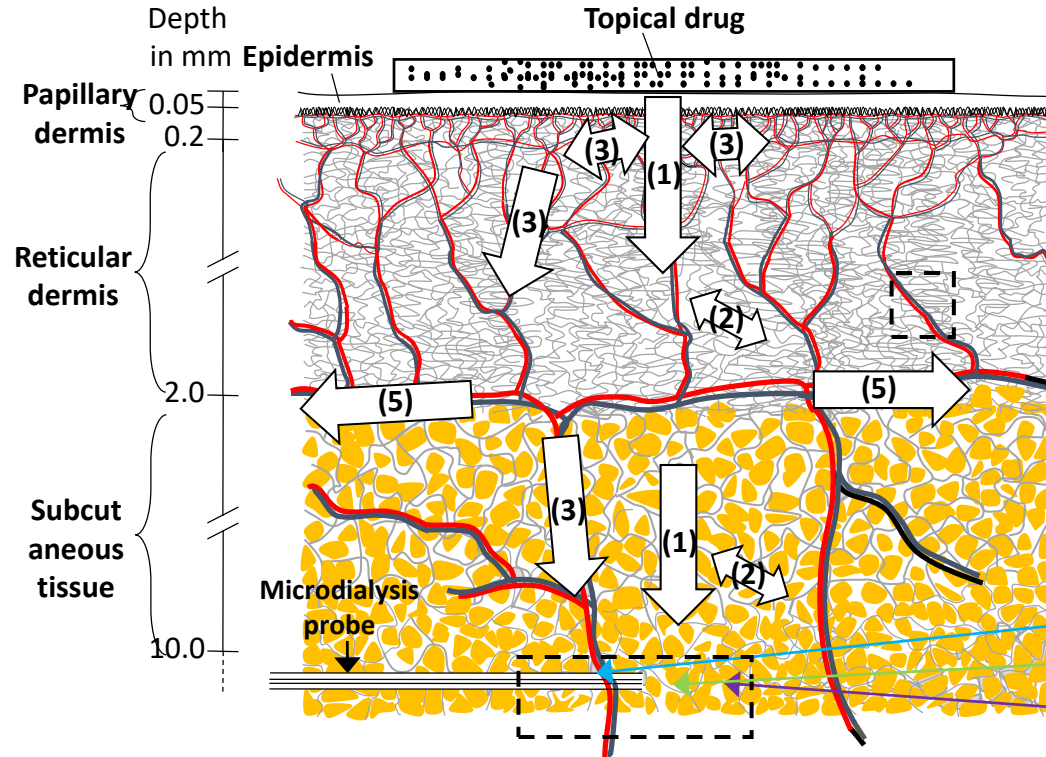
(Muller J Rheumatol 25, 1833, 1998)



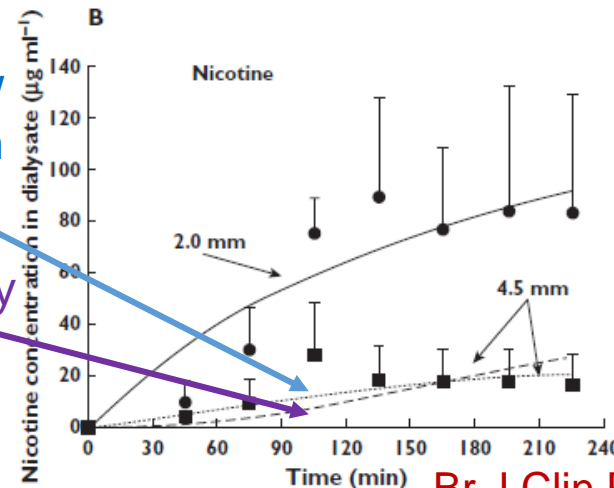
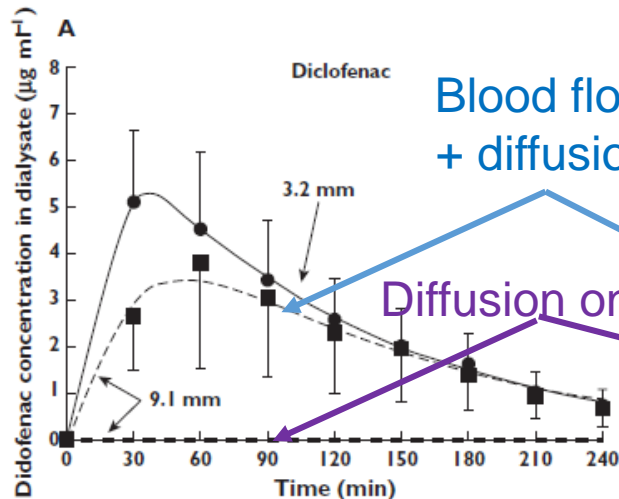
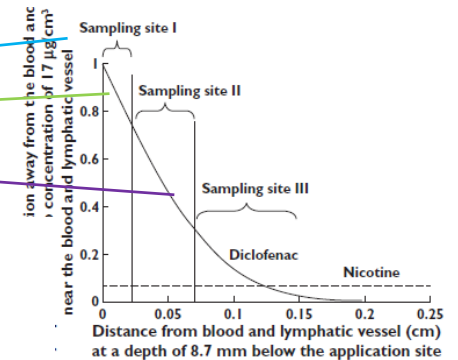
Similar synovial fluid diclofenac concentrations in treated and control in many studies (Rademacher et al 1991) & generally ~0.5 to 0.6 that for plasma, consistent with relative protein concentrations.



# Why does diclofenac penetrate so deep?



Transport either by diffusion in dermis and/or shunting by blood /lymphatics

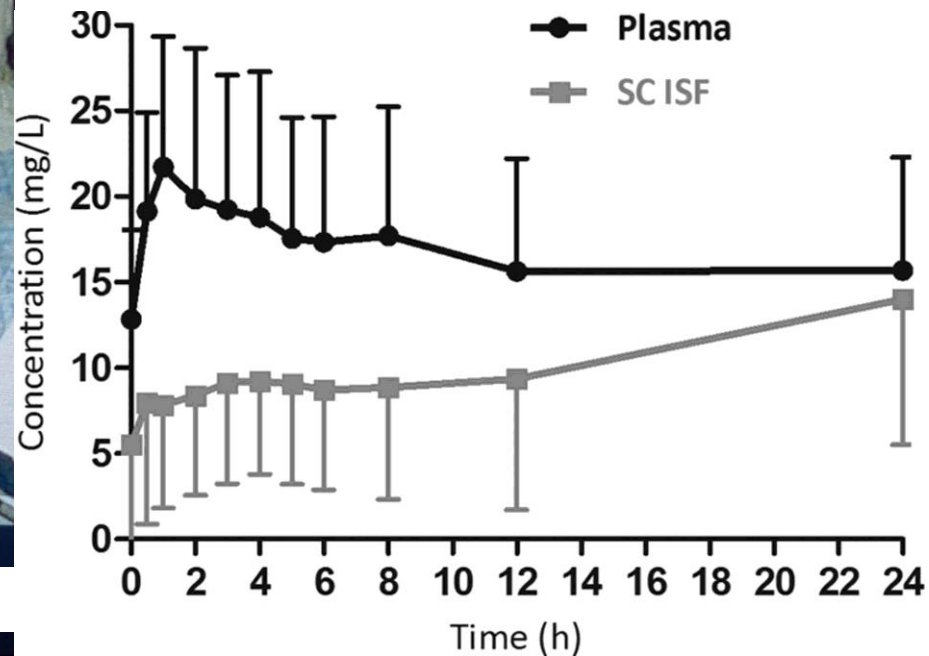


**Conclusion:**  
Highly plasma protein bound drugs can be shunted by blood vessels to deeper tissues

# Key microdialysis translation is monitoring of tissue antibiotic distribution in ICU



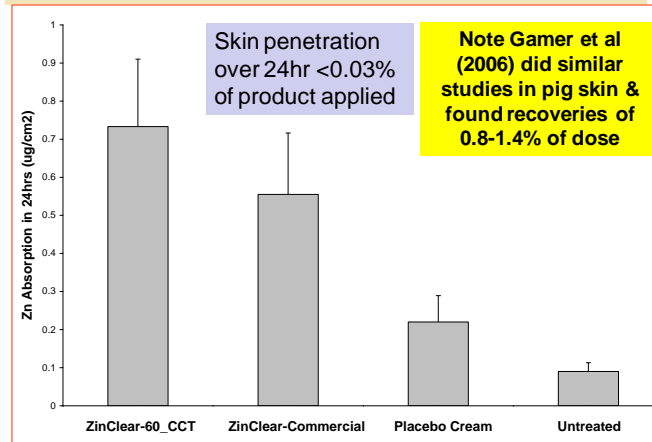
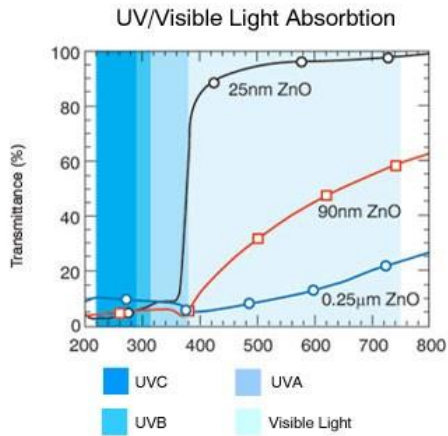
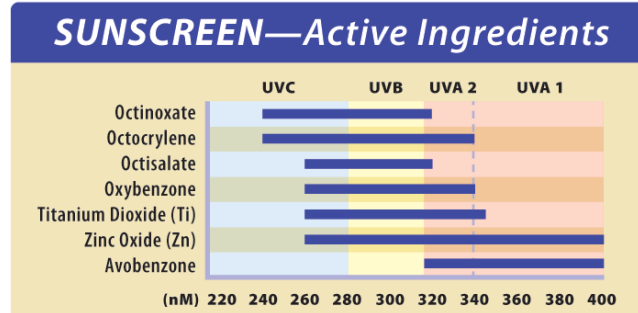
Free median (interquartile range [error bars]) plasma & SC ISF fluconazole concentration-time profile in critically ill patients after 400-mg dose.





# Safely preventing sun-induced inflammatory skin conditions, e.g. sunburn, actinic keratosis & photoaging

## Organic sunscreens versus nanoparticles - Queensland & its capital city, Brisbane, have highest world incidence of skin cancer



### Nano-ingredients in sunscreen

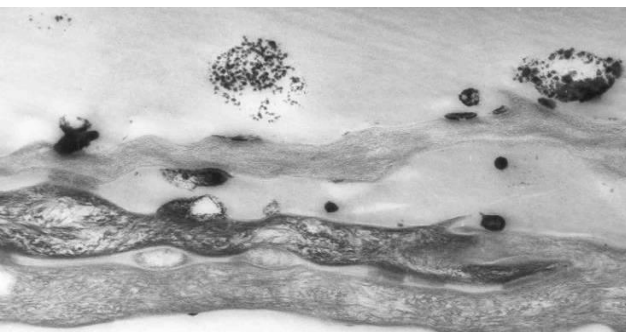
#### The need for regulation

July 2012

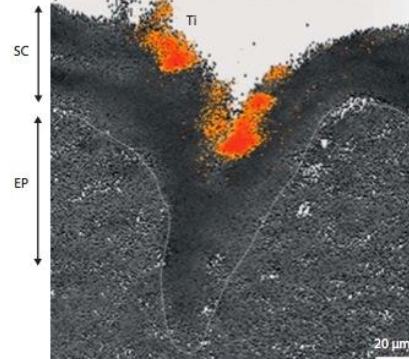
They won't put nano on the label, but they'll put it in your sunscreen.

**Take Action**

Tell the truth. Put nano on the label.



### Psoriatic skin TiO<sub>2</sub>



Cell culture: ZnO-NP (0.8 – 5 µg/ml) reduced cell viability, induced DNA damage and oxidative stress in human epidermal cell *in vitro* (0-24 hours treatment)



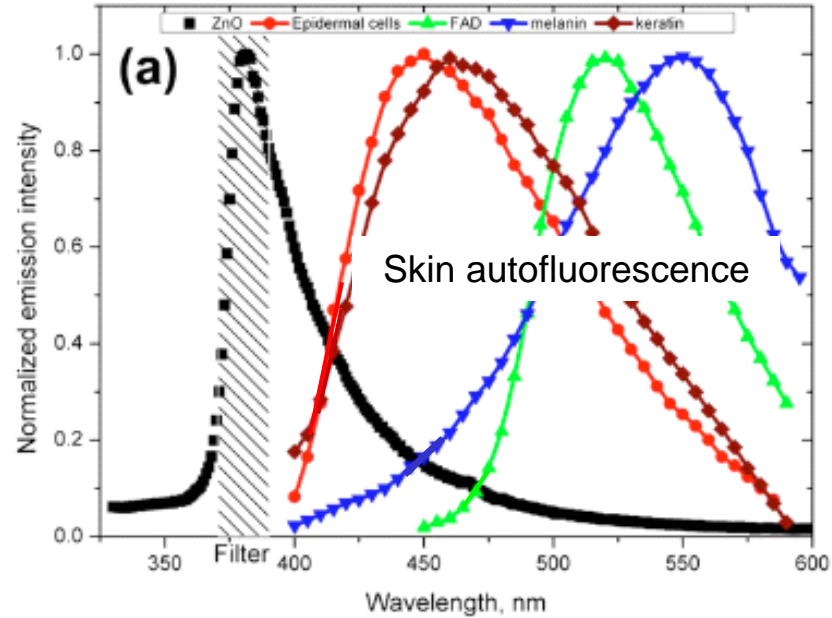
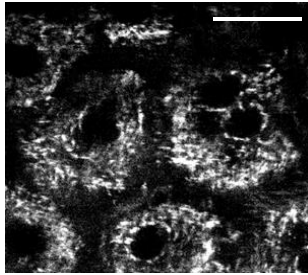
# In vivo: Non-invasive spectral imaging of human skin - *Dermalnspect*<sup>TM</sup>

## Penetration of sunscreen of Nano-zinc oxide in vivo



**fluorescence**

Two-photon fluorophore excitation with <math><2\text{mW}</math>, fs, 720-910 nm pulses (Mai Tai) i.e.  $\sim 360$  to 455nm confocal equivalent



Computerised filter wheel added

0 hr SC

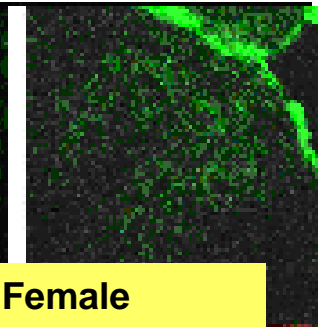
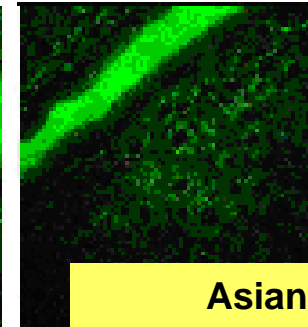
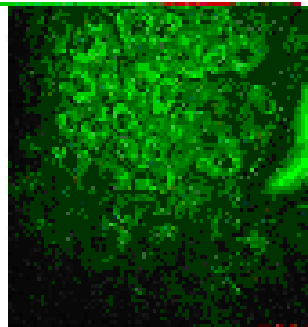
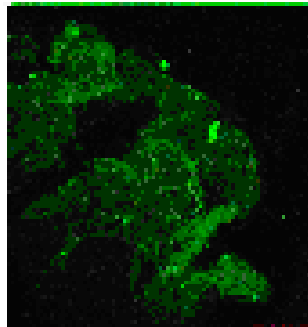
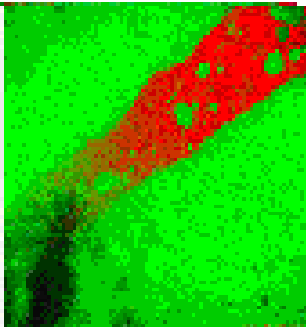
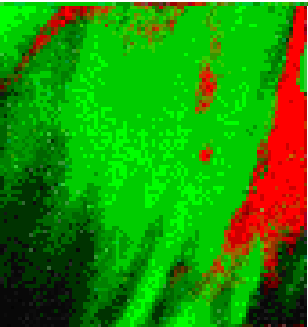
4 hr SC

24 hr SC

0hr Epidermis

4hr Epidermis

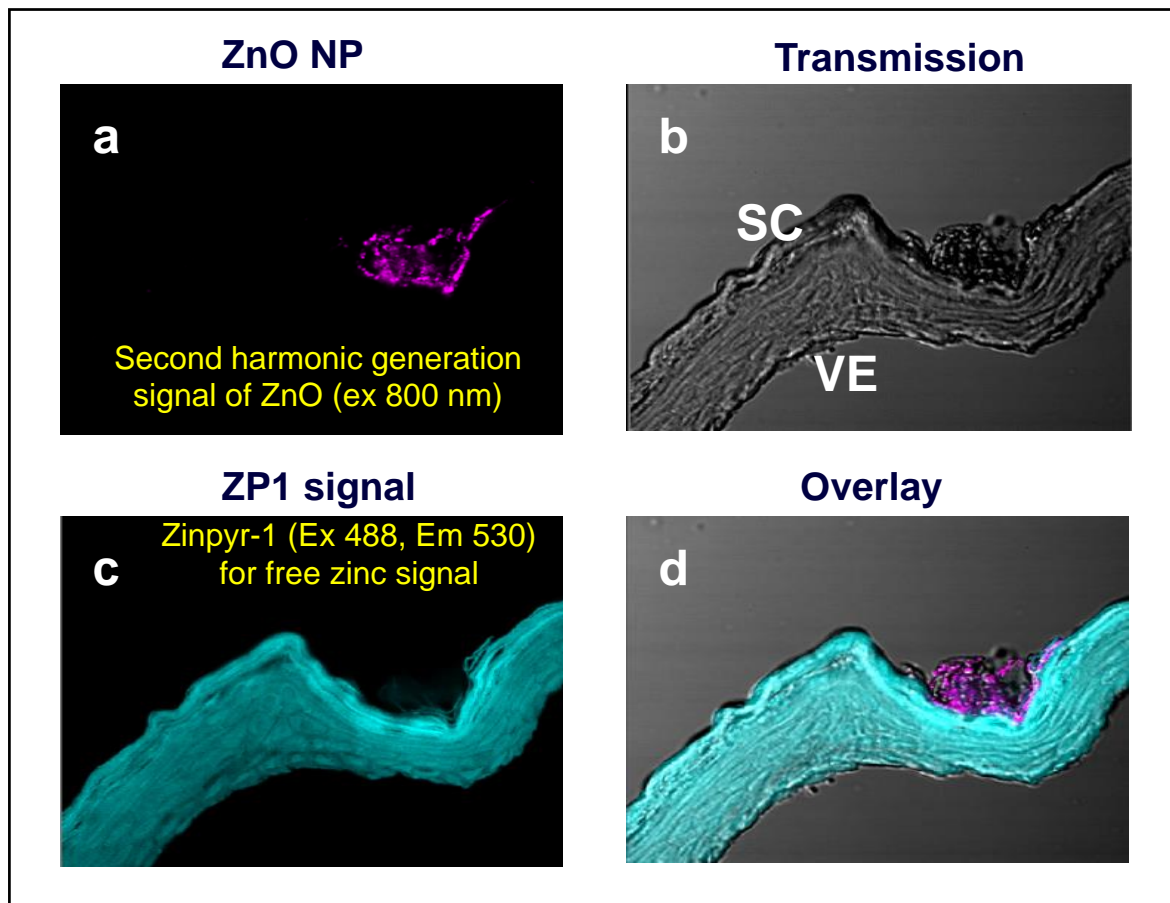
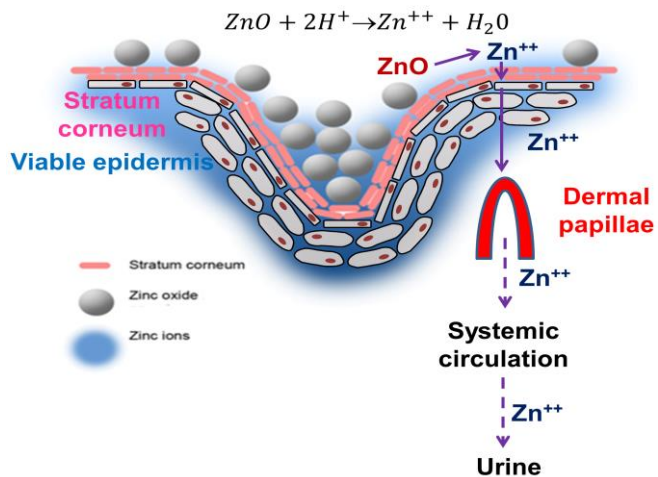
24hr Epidermis



Asian Female

# Preferential accumulation of ZnO nanoparticles within furrows of human skin

ZnO dosed in 10 % wt nanoZnO in CCT applied to HSE for 48 h cryosections are 10  $\mu\text{m}$  thick:



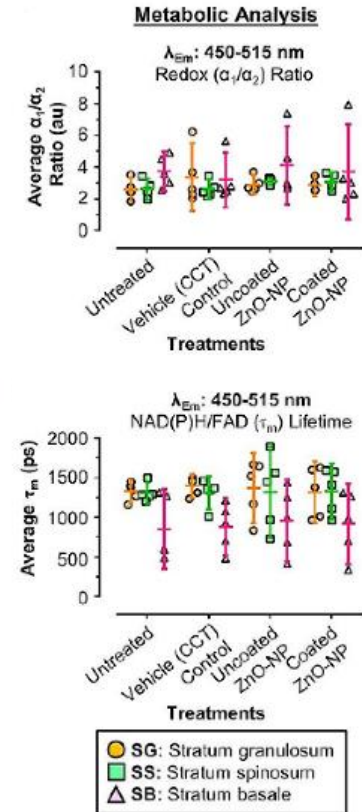
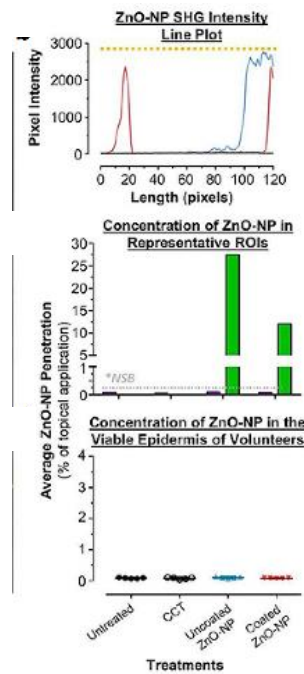
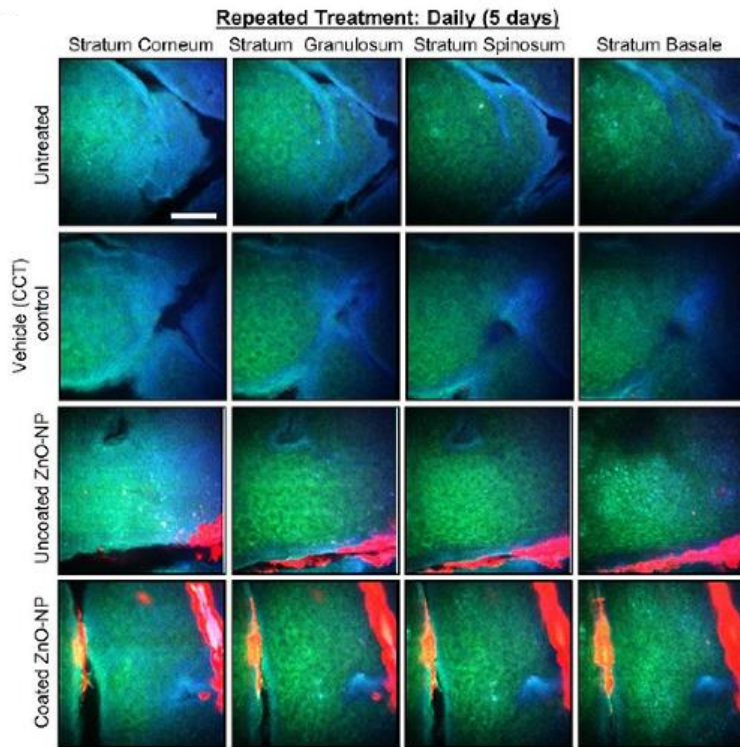
Likely basis for systemic  $\text{Zn}^{68}$  increases after topical ZnO to volunteers under in use conditions (Gulson et al.)

AM Holmes et al., *ACS Nano* **2016**, 10, 1810–1819

# Safe use of zinc oxide nanoparticle sunscreens in humans *in vivo*

Lack Of Skin Penetration

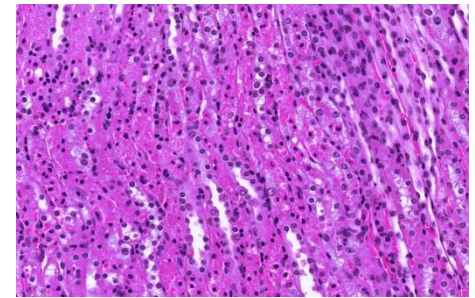
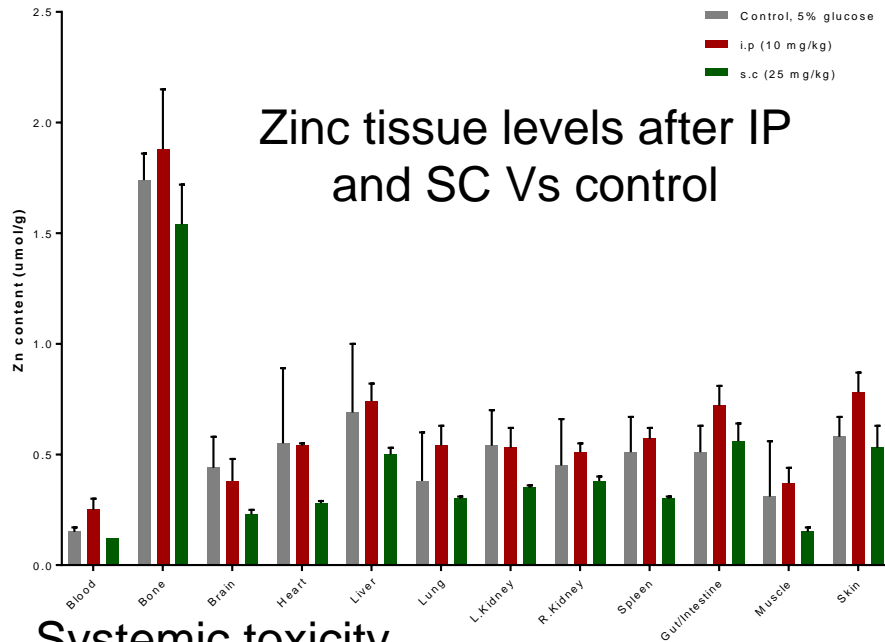
Lack of Cellular Toxicity



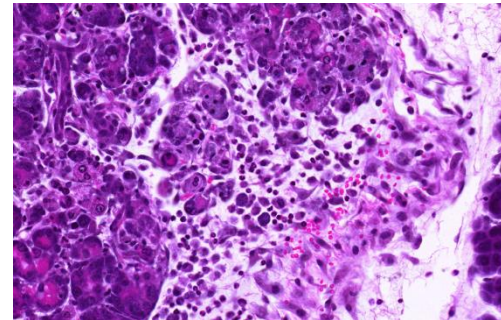
*J Invest Dermatol* 2019 - highest impact factor Dermatology journal  
**Message now to dermatologists that topical zinc oxide nanoparticles are safe**



# Systemic zinc oxide toxicity possible?

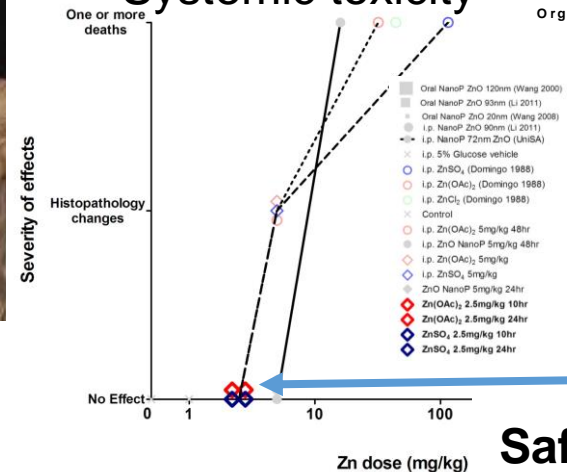


kidney - severe degeneration & necrosis of collecting tubules



pancreas - necrosis and apoptosis in the exocrine pancreas with some loss of acini and inflammatory cell infiltration

## Systemic toxicity



Gulson et al Toxicol In vitro <sup>68</sup>Zn tracer absorption from sunscreen applied to whole human body (1.8 m<sup>2</sup>) gives dose of 0.0045 mg/kg

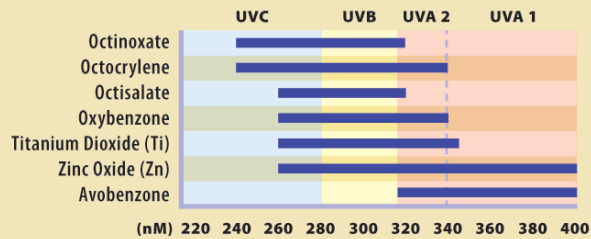
No observable effect ip dose in mice: 5 mg/kg

Safety factor = 5/0.0045 = 1,111 >> usual >100X

# Safely preventing sun-induced inflammatory skin conditions, e.g. sunburn, actinic keratosis & photoaging

## Organic sunscreens

### SUNSCREEN—Active Ingredients



Concerns have been raised about the safety and effects of chemical sunscreens on **endocrine, reproductive, developmental, and cancer-related outcomes**, as well as **environmental harm**.

FDA NEWS RELEASE

### FDA advances new proposed regulation to make sure that sunscreens are safe and effective

Propose of the 16 currently marketed active ingredients, only two – zinc oxide and titanium dioxide – are GRAS (generally regarded as safe) for sunscreens

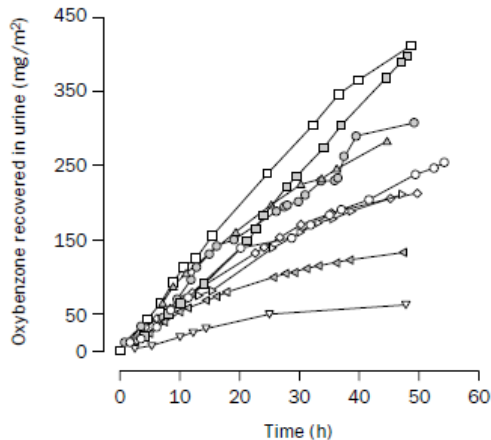
For Immediate Release:

February 21, 2019

### 1997 The Lancet

#### Systemic absorption of sunscreen after topical application

Cameron G J Hayden, Michael S Roberts, Heather A E Benson



Oxybenzone recovered in urine as unchanged oxybenzone and metabolites after topical application of commercially available SPF 15+ sunscreen to nine human volunteers  
1 m<sup>2</sup> is approximately 60% of an adult's total skin surface area (1.7 m<sup>2</sup>).

### Research

JAMA | Preliminary Communication

#### Effect of Sunscreen Application Under Maximal Use Conditions on Plasma Concentration of Sunscreen Active Ingredients A Randomized Clinical Trial

Murali K. Matta, PhD; Robbert Zusterzeel, MD, PhD, MPH; Nageswara R. Pilli, PhD; Vikram Patel, PhD; Donna A. Volpe, PhD; Jeffrey Florian, PhD; Luke Oh, PhD; Edward Bashaw, PharmD; Issam Zineh, PharmD, MPH; Carlos Sarabria, MD; Sarah Kemp, RN; Anthony Godfrey, PharmD; Steven Adah, PhD; Sergio Coelho, PhD; Jian Wang, PhD; Lesley-Anne Furlong, MD; Charles Ganley, MD; Theresa Michele, MD; David G. Strauss, MD, PhD

TRAVEL EXPLAINER

### What sunscreens are best for you—and the planet?



Is your sunscreen killing coral reefs?

Zinc oxide & titanium dioxide  
not ingested by coral

ing coral reefs? - CNN

# Consumer therapeutics and safety: from the outside looking in - summary

- Follow one's passions – we can all make a difference in our own way!
- Opportunities are to be seen and grasped, e.g. aspirin as an antithrombotic
- There is fun in working out why some medicines work better than others, e.g. topical NSAIDs
- If you believe in a cause stay with it, e.g. nano zinc oxide
- Outcomes may take many years to come to fruition, e.g. organic sunscreens
- New and & advancing technologies create new opportunities

*Whatever you can do or dream you can, begin it.*

*Boldness has genius, power and magic in it*

*Goethe*

