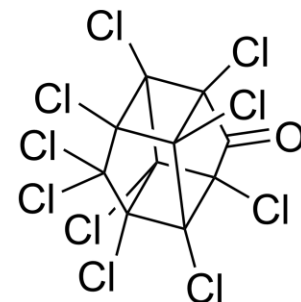


***IN VIVO* EFFECTS OF TWO CHLORDECONE DERIVATIVES, OBTAINED BY *IN SITU* CHEMICAL REDUCTION, IN A HUMAN PROSTATE MODEL**

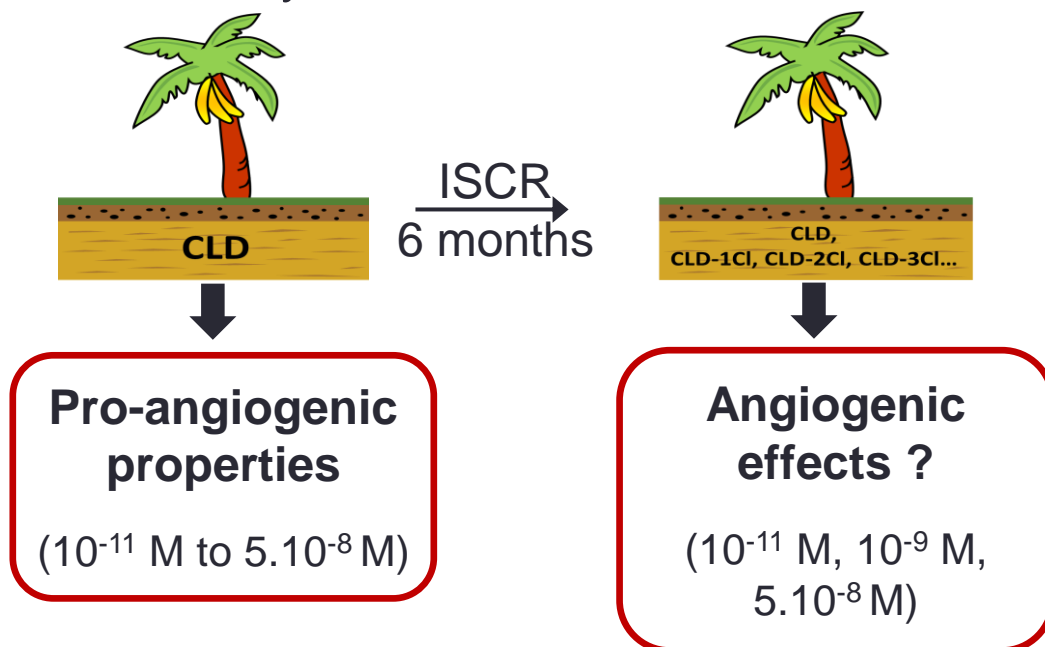
Pierre-André Billat
GFP 2017



Introduction

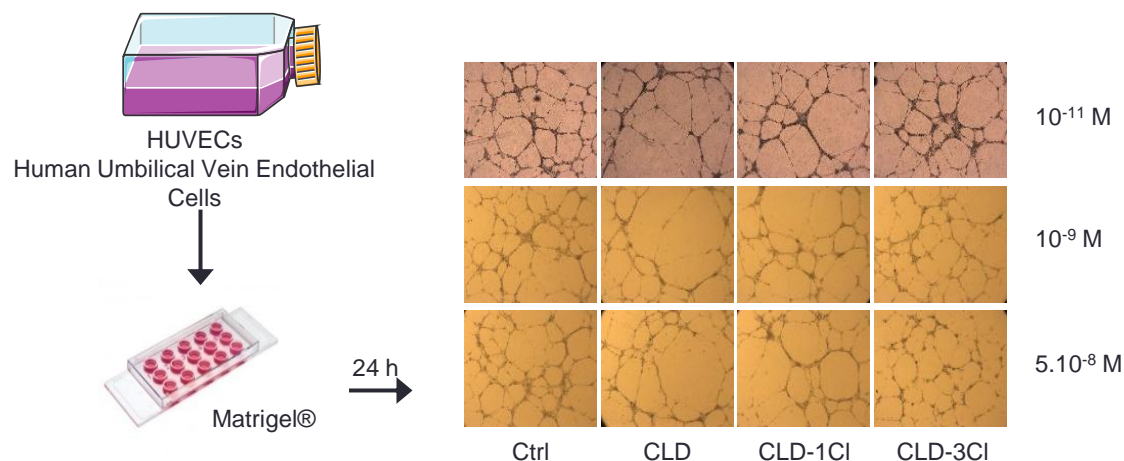


- Chlordecone (CLD) POP
- Found in the edible roots and the water of French West Indies
- Association between the development of prostate cancer and CLD exposure (angiogenesis)
- *In Situ* Chemical Reduction (ISCR) possible way for the remediation of soils contaminated by CLD



Context

- Mono-hydroCLD (CLD-1Cl) and tri-hydroCLD (CLD-3Cl) have lower cytotoxicity and proangiogenic properties than CLD itself*



HUVECs treated by CLD or CLD-1Cl or CLD-3Cl at 10^{-11} M (concentration of CLD in drinking water), 10^{-9} or $5 \cdot 10^{-8}$ M (plasmatic concentration of exposed humans) for 24 hours

**Two dechlorinated chlordane derivatives formed by in situ chemical reduction are devoid of genotoxicity and mutagenicity and have lower proangiogenic properties compared to the parent compound. Legeay S et al., Environ Sci Pollut Res Int. 2017*

Hypothesis / Objectives

- Have CLD-1CI and CLD-3CI similar lower cytotoxicity and proangiogenic properties than CLD itself *in vivo* ?
- The present study aims at:
 - exploring the angiogenic properties of the two CLD derivatives on a prostate cancer model *in vivo*
 - comparing the serum levels of exposure of CLD and each derivative, 24h post intake

M&M

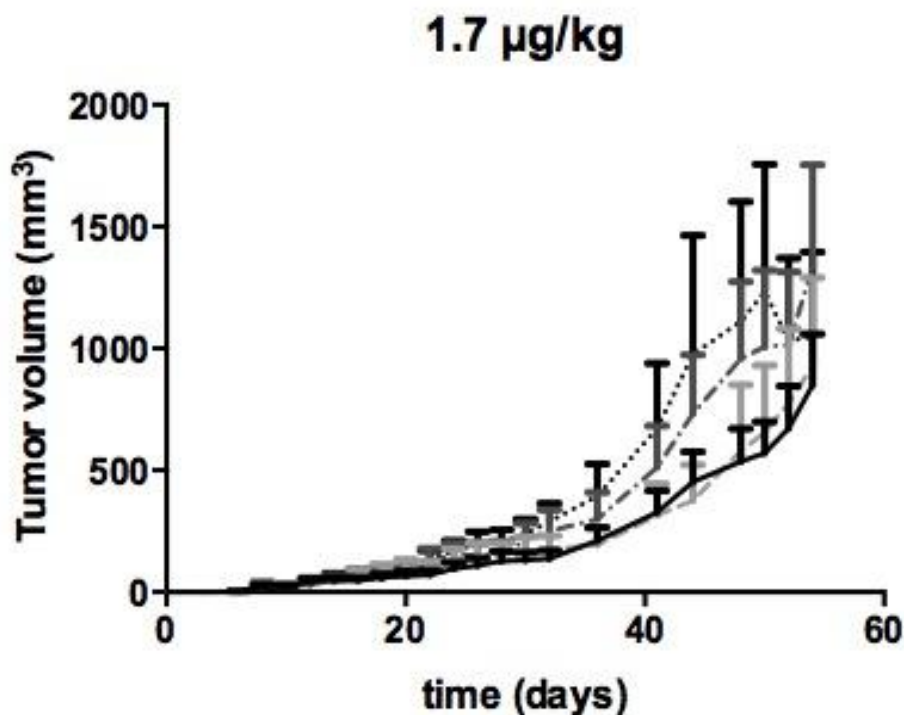
- 1.5×10^6 cancerous human prostate (PC3) cells
- 38 nude athymic mice
- Animals were exposed to the pesticide or its derivatives at two doses: 33 $\mu\text{g}/\text{kg}$ (body weight) (n=17), or 1.7 $\mu\text{g}/\text{kg}$ (n=15), or olive oil (control, n=6), by daily gavage for 7 weeks.



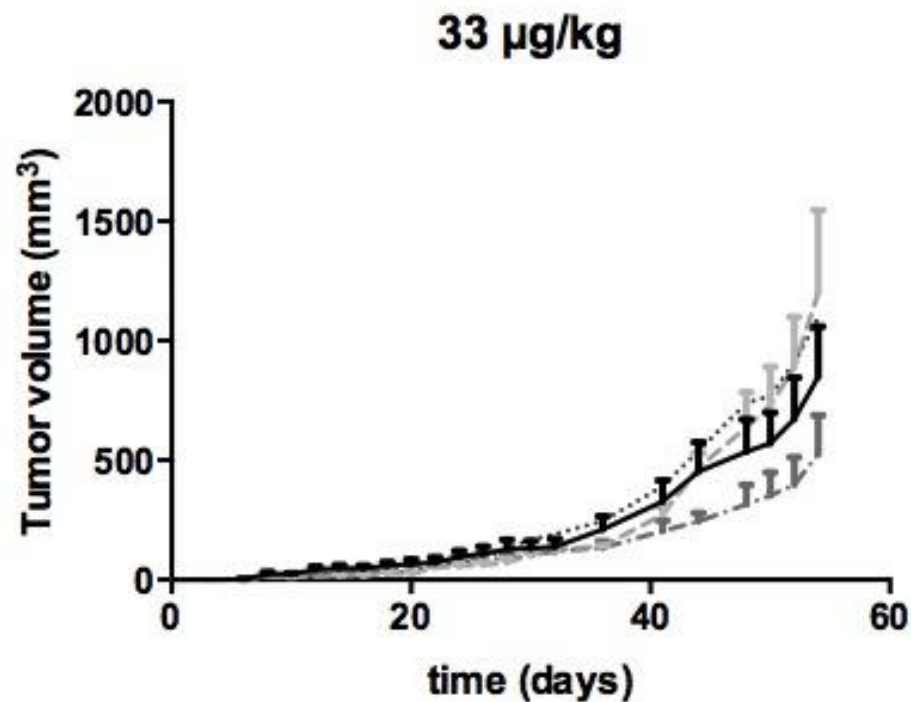
Nude mice treated *per os* by CLD or CLD-1Cl or CLD-3Cl at 1.7 $\mu\text{g}/\text{kg}$ (to reflect human exposure), or 33 $\mu\text{g}/\text{kg}$ (high exposure in humans) for 8 weeks

Results (1)

- No effect of the metabolites on tumor growth vs control



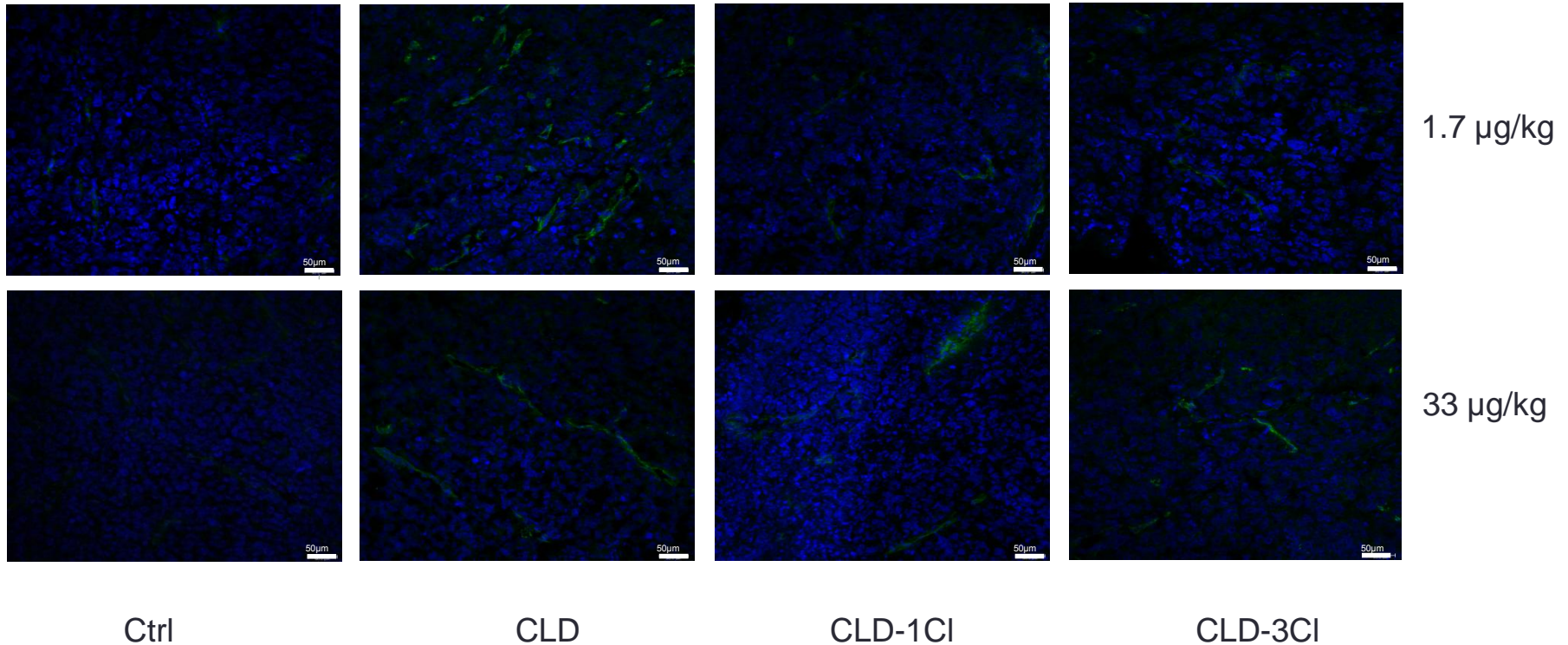
— Control (n=6)
- - - CLD (n=3)
- · - CLD-1Cl (n=3)
····· CLD-3Cl (n=5)



— Control (n=6)
- - - CLD (n=3)
- · - CLD-1Cl (n=6)
····· CLD-3Cl (n=1)

Results (2)

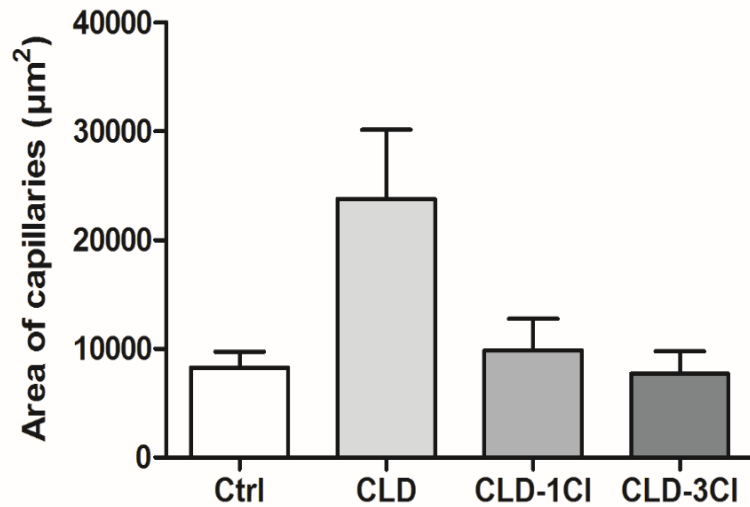
- Immunostaining of tumor endothelial cells (green)
- Nucleus (blue)



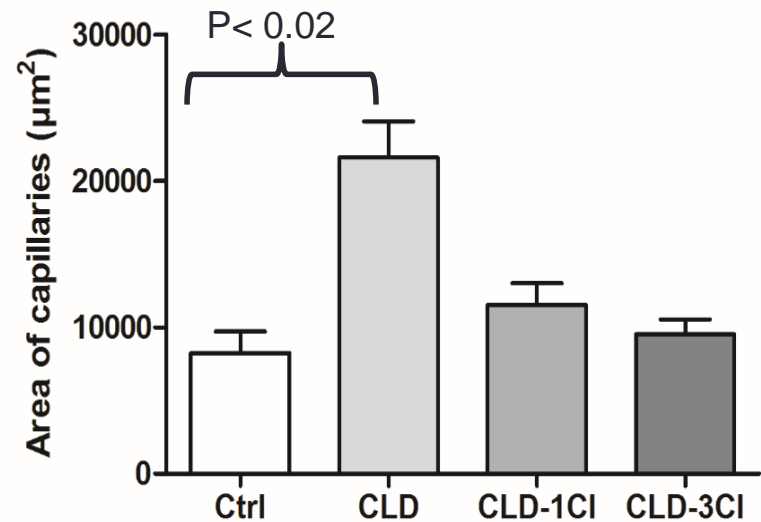
Results (2bis)

- Immunostaining of tumor endothelial cells (green)
- Nucleus (blue)

1.7 $\mu\text{g}/\text{kg}$



33 $\mu\text{g}/\text{kg}$



Results (3)

- Measurement of CLD, CLD-1Cl and CLD-3Cl in plasma 24h post dose
- LC-MS/MS method*

	Serum concentration (M)	
	33 µg/kg	1.7 µg/kg
CLD	$2.7 \cdot 10^{-7} \pm 1.6 \cdot 10^{-8}$	$1.1 \cdot 10^{-8} \pm 4.0 \cdot 10^{-9}$
CLD-1Cl	$4.5 \cdot 10^{-8} \pm 4.0 \cdot 10^{-9}$	$5.2 \cdot 10^{-9} \pm 1.1 \cdot 10^{-9}$
CLD-3Cl	$6.2 \cdot 10^{-9} \pm 1.2 \cdot 10^{-9}$	$< 8.0 \cdot 10^{-10}$

Serum concentrations of CLD-1Cl and CLD-3Cl are lower than CLD concentrations

→ Different behavior in the organism

*Bichon E et al.. Ultra-trace quantification method for chlordecone in human fluids and tissues. J Chromatogr A. 2015

Conclusion

- **CLD favors angiogenesis** in both *in vivo* and *in vitro* models
- CLD derivatives obtained by ISCR have a **decreased pro-angiogenic effect** compared to CLD *in vitro* and *in vivo*
- **Exposure to the derivatives in mice serum is lower** than exposure to CLD
- ISCR is a promising process for the remediation of soils contaminated by this pesticide
- Further studies are required to confirm these results in another cohort of mice

Contributors

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