DDA, A Water-soluble Metabolite Of DDT

Zhenshan Chen, Yanhong Li, Melinda Bigelow Dyk, Francois Maartens, Helen Vega, Bob Krieger

Personal Chemical Exposure Program
Environmental Toxicology Graduate Program

Department of Entomology
University of California, Riverside

Controversial use of DDT

- DDT is prototype POP
- Global transport and widespread exposure
- *Silent Spring* elevated “exposure” to a health concern
- Analysis at low levels became easy

Introduction of DDT into the U.S.

- In August 1942, Froehlicher, Ciba-Geigy received ‘Gesarol’ spray and dust from Switzerland
- Jonge, U.S. Army great interest in ‘Neocid’ against body lice and typhus
- October 1942 insecticidal activity for ag pests disclosed reports from Swiss Agricultural Station to Roark, U.S.D.A.
- Confirmed by Haller et al. at Beltsville in 1945 (colormetric determination of DDT)

DDT use history

1940---Typhus control by Italian military

1940s--Save millions of lives in malaria control

1945---DDT found in milk and urine

1962---*Silent Spring*

1972---Banned by USEPA

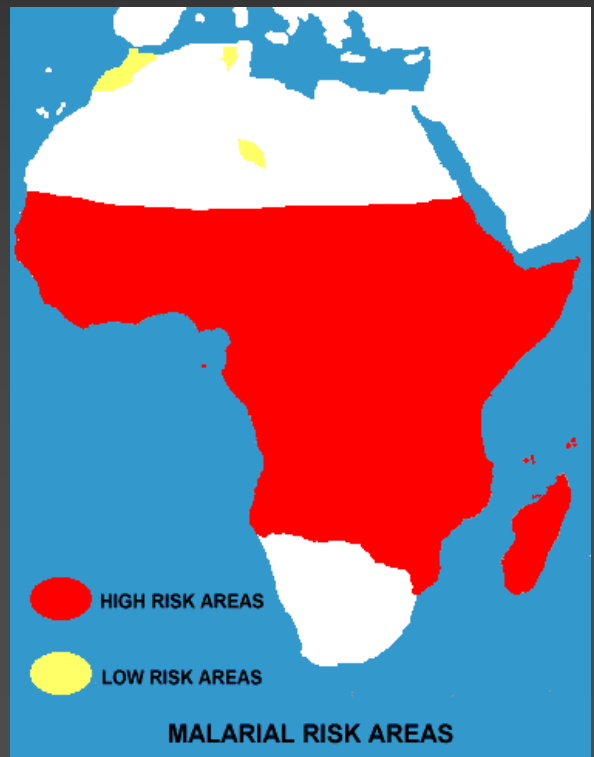
2004---Global ban as POP

DDT use in fighting malaria **today**

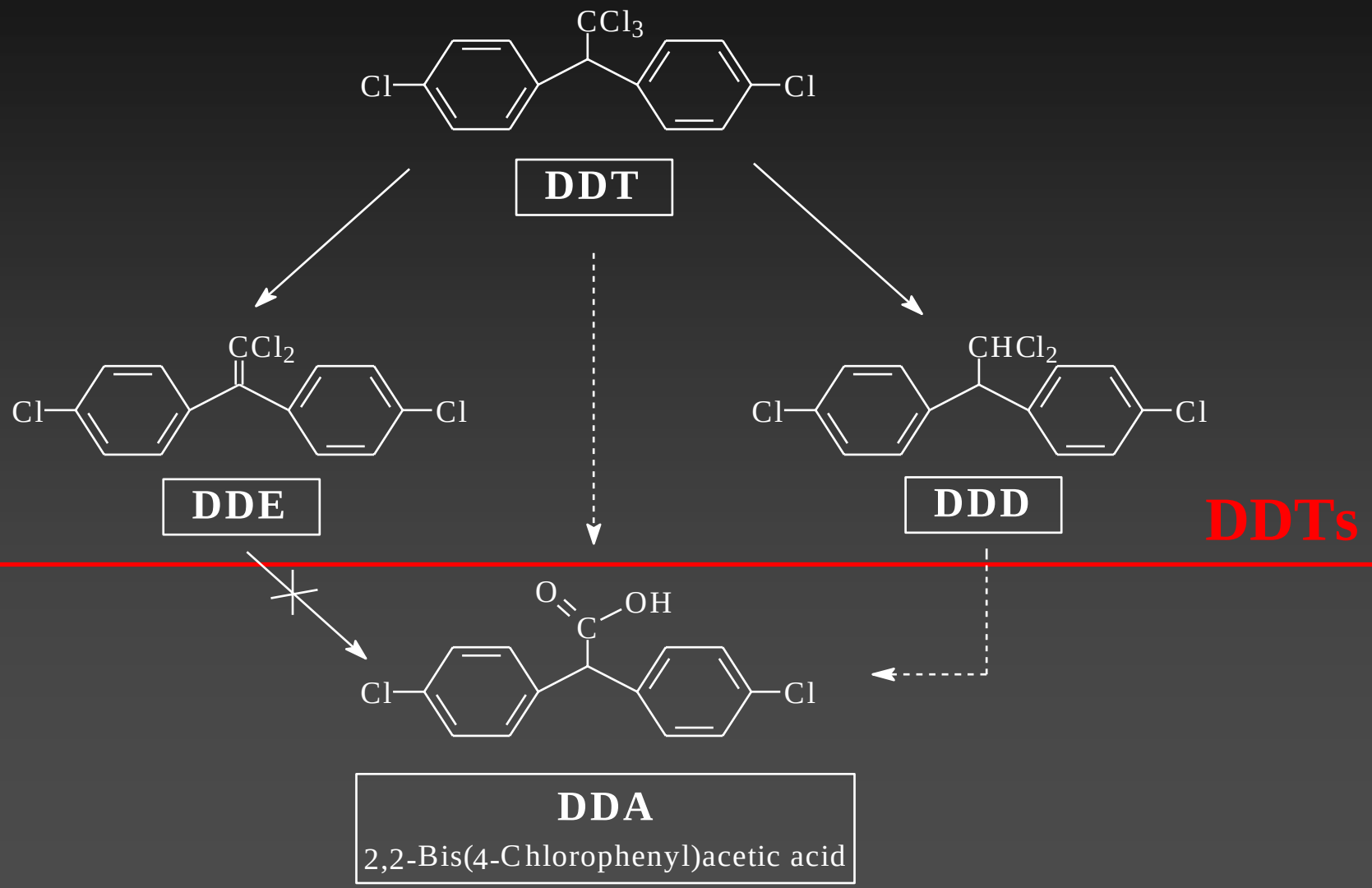
(*Indoor Residual Spraying* advocated by WHO)

WHO advocates DDT use

- Early dramatic success expanded to global public health
- Initially sanction in 2000 even though a POP
- In 2006 advocate use as cheap, effective in malaria control



DDT Metabolism and Biomonitoring



Preview

- DDT and DDA
- Urine biomarker analysis
- DDA urinalysis of DDT applicators
- Advancing DDT exposure assessment

DDT and DDA

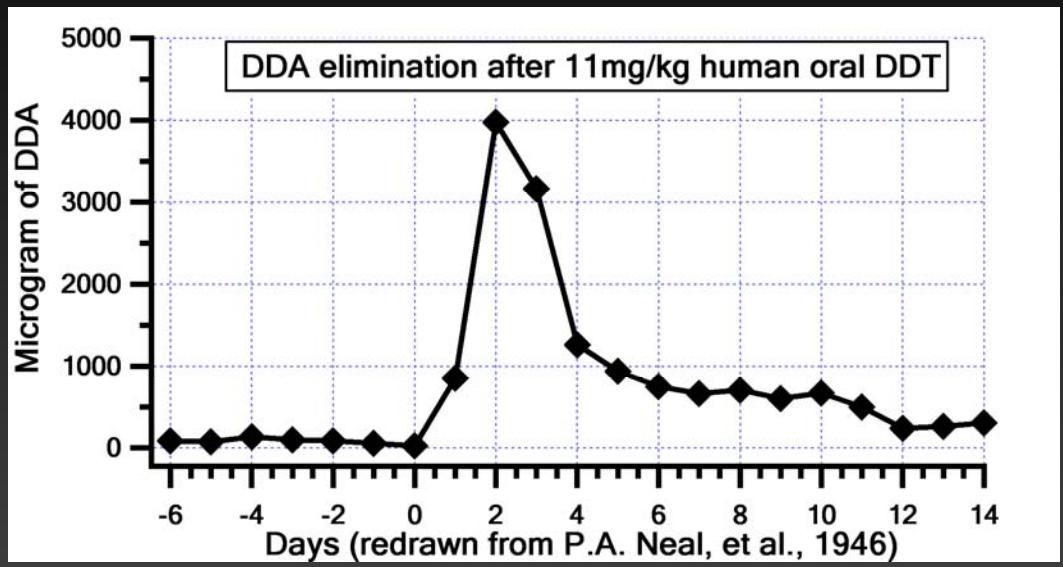
Disposition and Fate of DDA

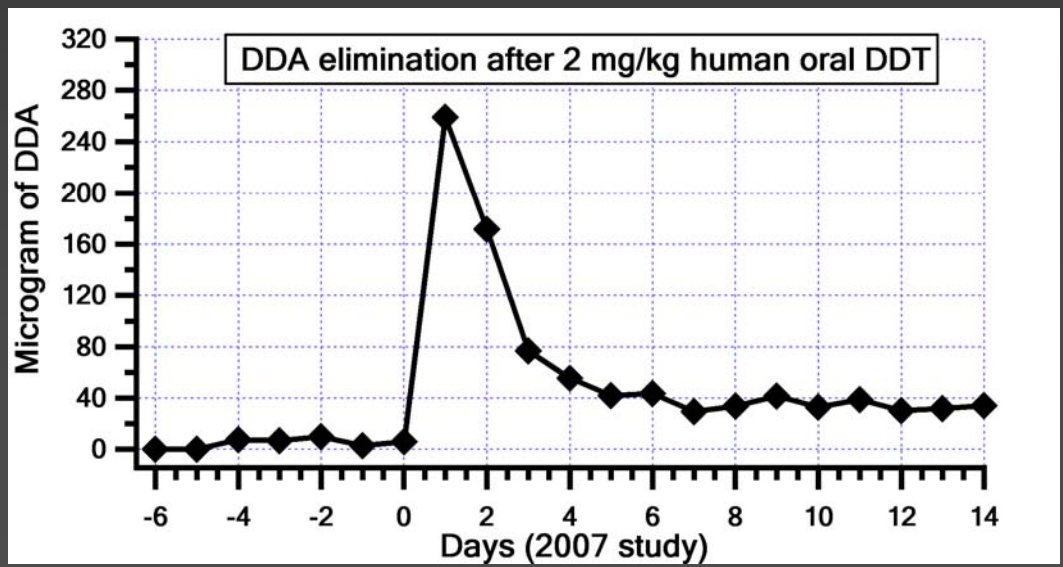
- DDT metabolism to DDA known in rabbits and human by 1946
- *Water-soluble*
- *Low toxicity*
- *Excreted in urine*
- Regulatory attention to lipophilics that were present in milk and later readily detected by electron capture gas chromatography

DDA excretion in urine

- 1946 DDT oral human study
- 1956 Hayes human study
- 1971 Morgan and Roan study
- 1970s UC Davis study

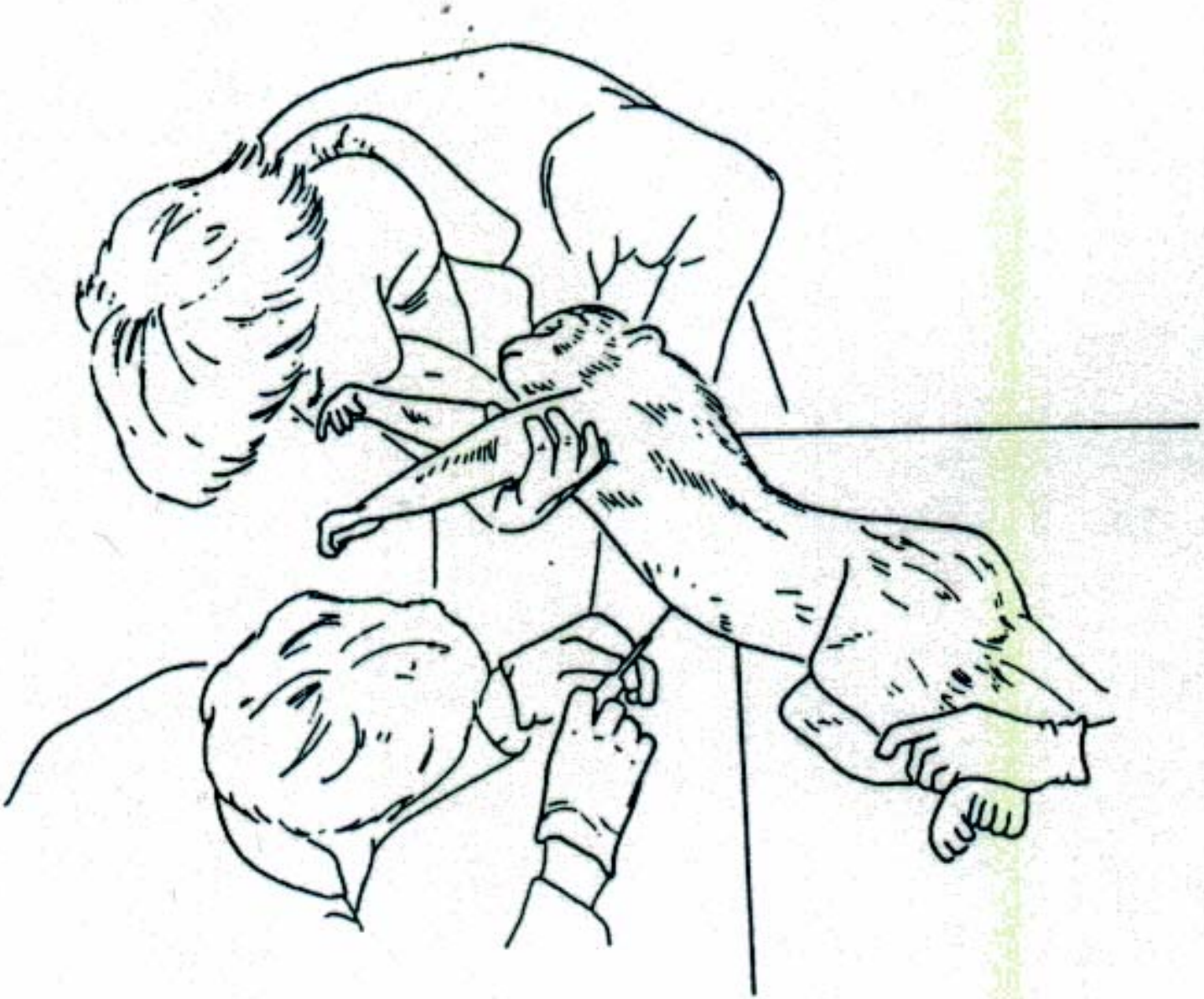
Urine DDA excretion in 1946 and 2007 studies





Morgan and Roan, 1971

- Oral doses of DDT, DDE, DDD, and DDA
- DDA excretion within 24 h after oral DDT, DDD, and DDA
- DDA to predose levels within 2-3 days after dose termination
- DDA significantly above predose levels for over 4 months



---Miller and Clark (UC Davis, 1977)

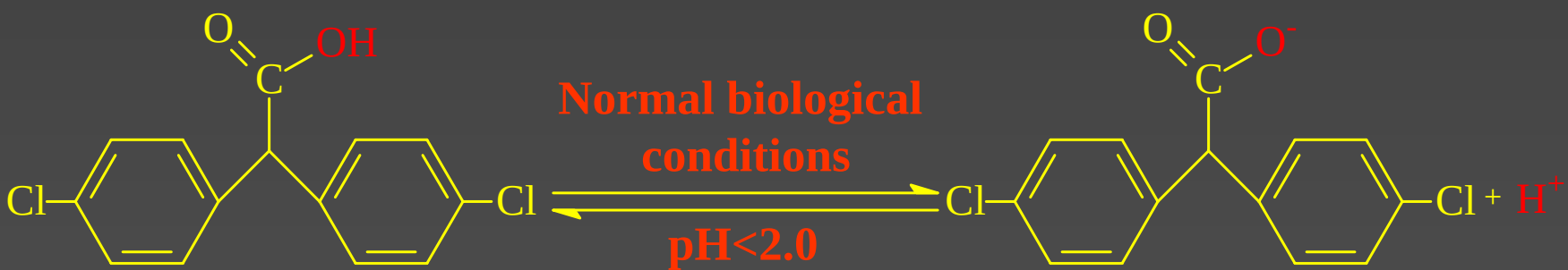
Modern exposure assessment stresses biomonitoring

- High level DDA excretion in urine of laboratory monkey during DDT feeding study
- Disappearance of DDA within days after stopping feeding
- Consistency with other DDT occupational studies

DDA in urine can be a good biomarker of concurrent DDT exposure!

Why has DDA been ignored?

- DDTs appearance in milk and fat
- DDA was proved to be relatively non-toxic
- Extraction of DDTs in biological samples by organic solvent miss DDA



fat soluble

water soluble

DDT Biomarkers

- DDTs (DDT,DDE,DDD)
  - Blood
  - Fat
- Lipophilic
- Long half-life
- Very different toxicology

- DDA
  - Urine
- Hydrophilic
- Short half-life
- Kidney target organ

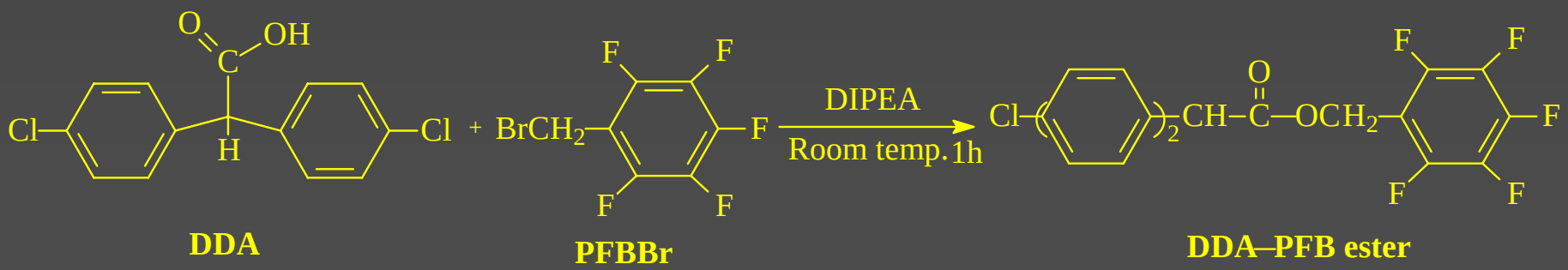
Urine Biomarker Analysis

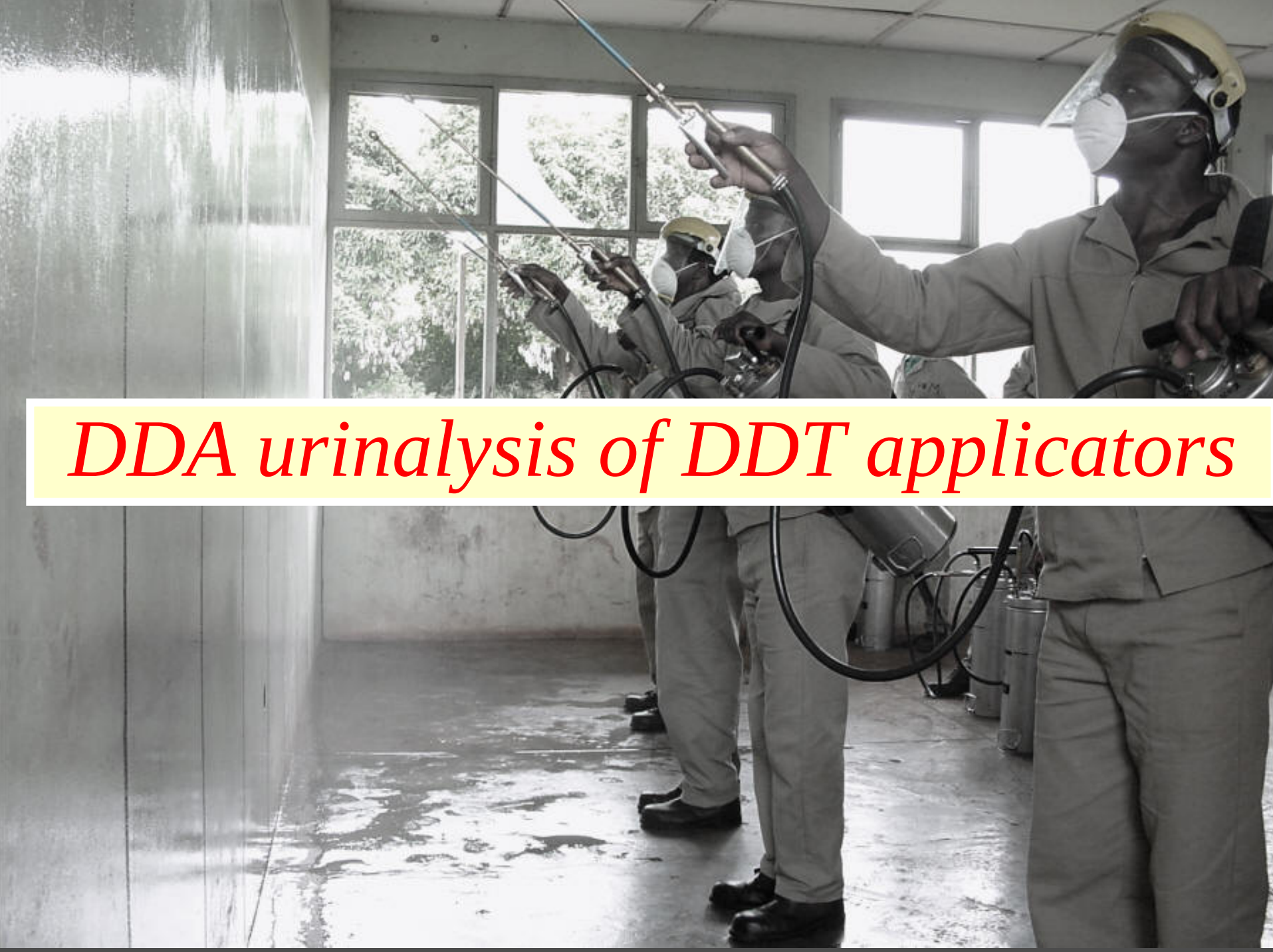
What we do?

Biomonitoring DDT exposures of applicators and local residents in anti-malaria campaign by using DDA as a biomarker.

DDA Derivatization and Analysis

- pH adjustments (>10 and <2.0) so that DDTs and DDA can be extracted one after another
- Liquid-Liquid Extraction with hexane
- Derivatization of DDA part with PFBBr and DIPEA
- Analysis by GC-ECD and confirm by GC-MS
- LOD for DDA analysis is 2 ppb



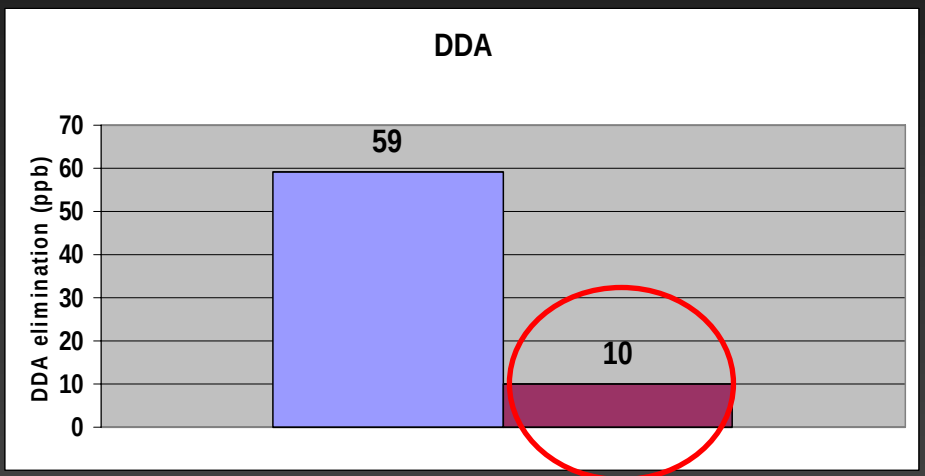


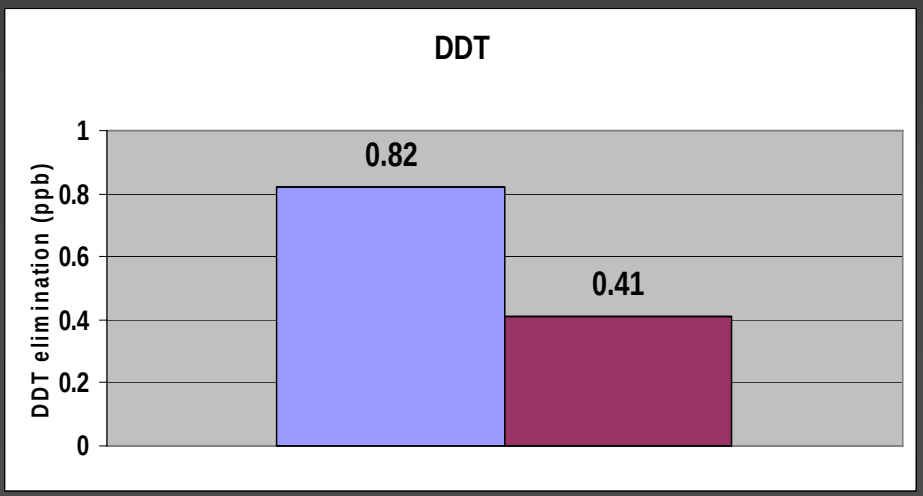
DDA urinalysis of DDT applicators

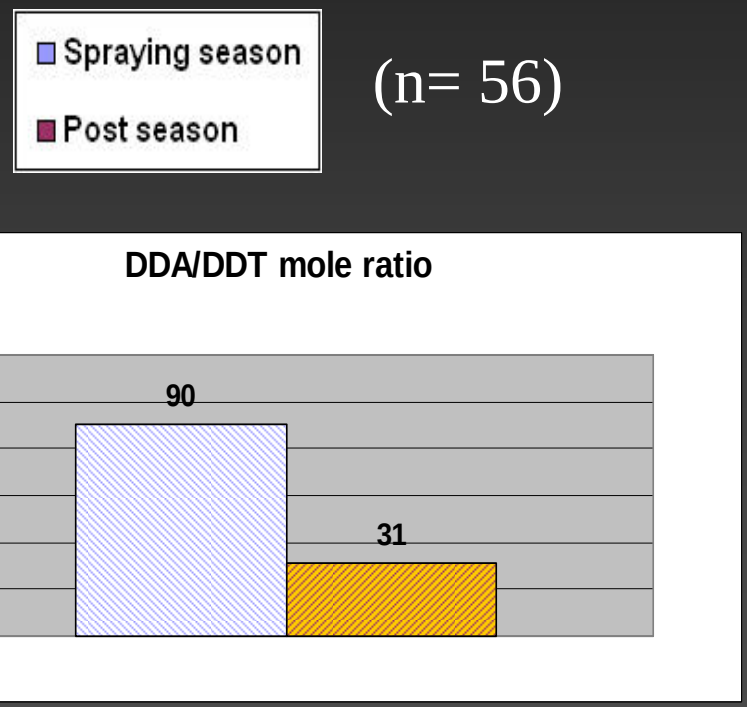
DDT applicator samples from Africa

- Sample collection and transportation by local collaborators in Swaziland and South Africa
- Spray season samples (Dec. 2007 & Mar. 2008)
- Post-season samples (Apr. 2008)

Results of Applicator Samples







(n= 56)

Biomarker for Surveillance and Monitoring

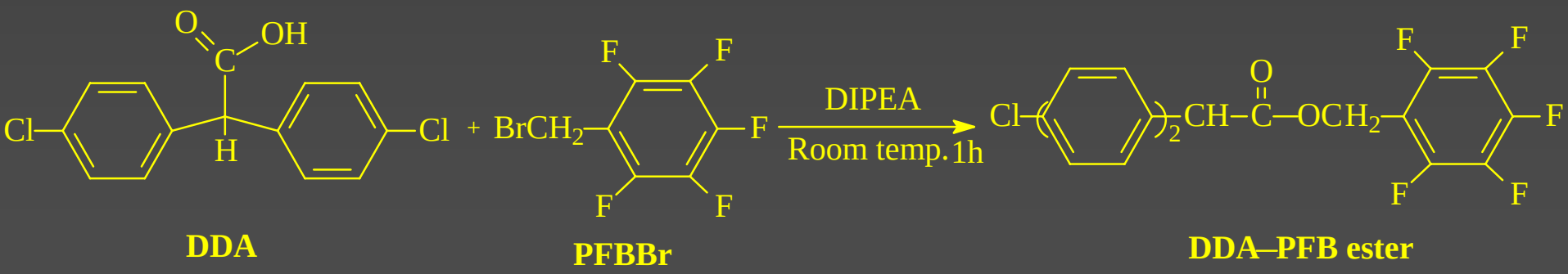
- Development of a simple, sensitive method to detect DDA in urine
- Repeat a 1946 human oral DDT study
- Pilot study on DDT applicators in Africa
- Clarify patterns of use and possible abuse

In Conclusion…

Advancing DDT exposure assessment

DDA urinalysis-- useful new tool for forensic analysis of DDT exposure

- Small urine samples (5-10 ml)
- Stable and relatively simple (1 hour R.T. reaction)
- Reproducible (R.S.D.= 12%)
- Sensitive (LOD= 2 ppb)
- Represents active DDT exposure



DDA **PFBBr** **DDA–PFB ester**

Toxicology of DDT, DDE and "DDTs"

- "DDTs" represents a complex mixture-analytically convenient,

  but misleading
- DDE is most persistent in fat tissue
- DDE LD50 880 mg/kg

- DDT and DDD exposures are readily converted to DDA
- DDA is readily excreted in urine
- DDT LD50 113 mg/kg; DDA LD50 740 mg/kg

  (kidney)

Continuing studies…

- Longitudinal prospective study among DDT applicators; expand to residents of treated homes
- Estimate primary DDT exposure (internal dose) by DDA excretion (24 h)
- Clarify exposure issues in environmental studies in humans and wildlife

Acknowledgments

- DDT applicators and assistants in Africa
- Unrestricted grants-in-aid to the UC Riverside, Personal Chemical Exposure Program
- Richard Tren, *Africa Fighting Malaria* and Don Roberts
- Simon Kunene, *National Malaria Control Manager, Swaziland*
- J.K Gumede, *Malaria Control Manager, KwaZulu-Natal, South Africa.*