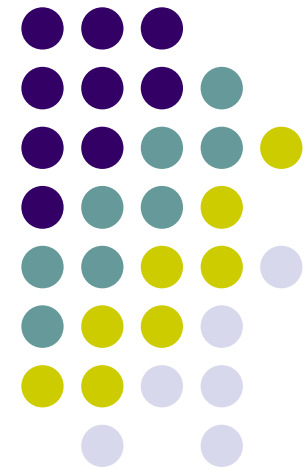


A Summary of ILSI and HESI Projects on the Threshold of Toxicologic Concern (TTC)

Susan Felter, Ph.D.
Central Product Safety
Procter & Gamble

ILSI-Japan Symposium
Tokyo, Japan

December 9, 2010

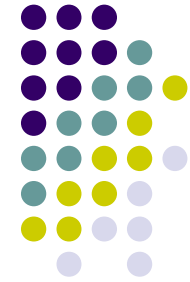




TTC Projects

- **ILSI NA**
 - **Refining TTC as tool for prioritization of food contaminants**
- ILSI Research Foundation
 - Extending TTC to support risk assessment of biocides
- HESI-Mixtures
 - TTC as a tool in mixtures risk assessment
- ILSI Europe
 - TTC Task Force

ILSI-NA: Refining TTC as tool for prioritization of food contaminants



“Okay—who put my lunch through the mass spectrometer..?”



Two areas of refinement

1. Refinement of tier for chemicals with structural alerts for genotoxicity, but negative Ames data

TTC Tiers

Genetox alerts: 0.15 ug/d

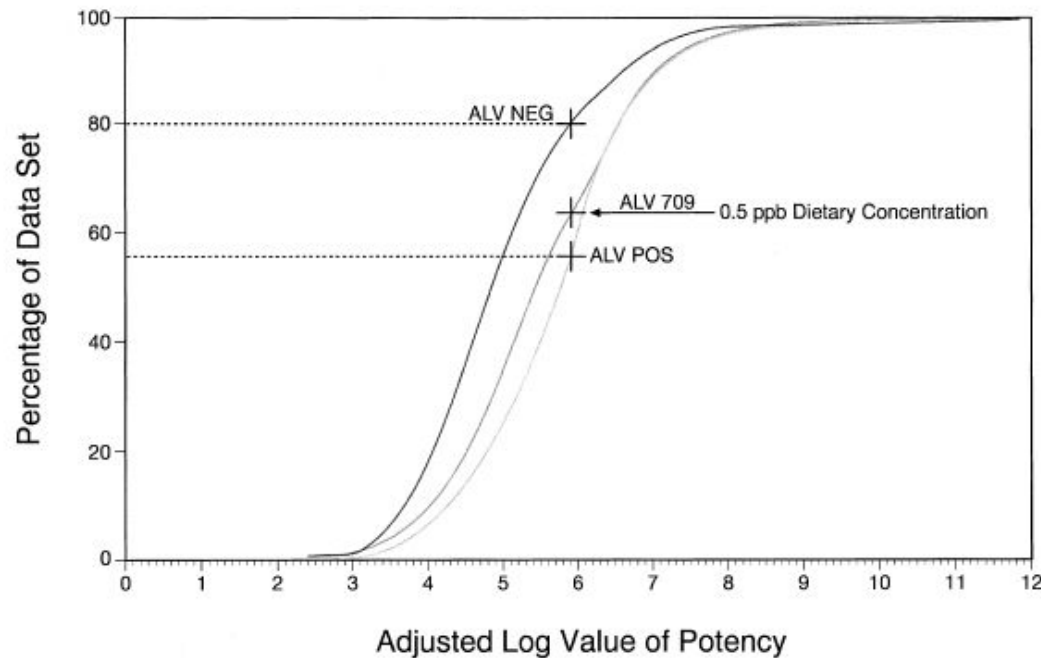
No alerts: 1.5 ug/d

2. Support for higher TTC tier for exposures not exceeding a year

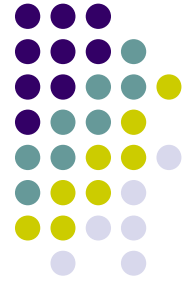
1. Incorporating genetox (Ames) data into TTC



- Cheeseman et al. (1999) determined that substances testing negative in the Ames test have cancer potency about an order of magnitude lower than Ames positive carcinogens.



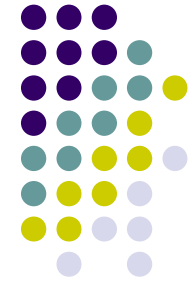
2. Support for higher TTC tier for exposures not exceeding a year



- Current TTC exposure limits are based on an assumption of lifetime exposure. This is appropriate for many applications, but overly restrictive for situations in which exposures are limited to shorter periods of time.
- US EPA cancer risk assessment guidelines are based on an assumption that lifetime cumulative dose (LCD) is the appropriate dose metric, such that higher exposures for shorter durations are equivalent to lower exposures for longer durations

$$C1 \times T1 = C2 \times T2 \text{ (“Haber’s rule”)}$$

Refining the cancer-based TTC exposure limit (0.15 ug/d)



- Strictly interpreted, for an exposure limited to 1 year, the magnitude could be 70 times the limit for daily exposures over a lifetime

$$0.15 \text{ ug/d} \times 70 \text{ yrs} = 10.5 \text{ ug/d} \times 1 \text{ year}$$

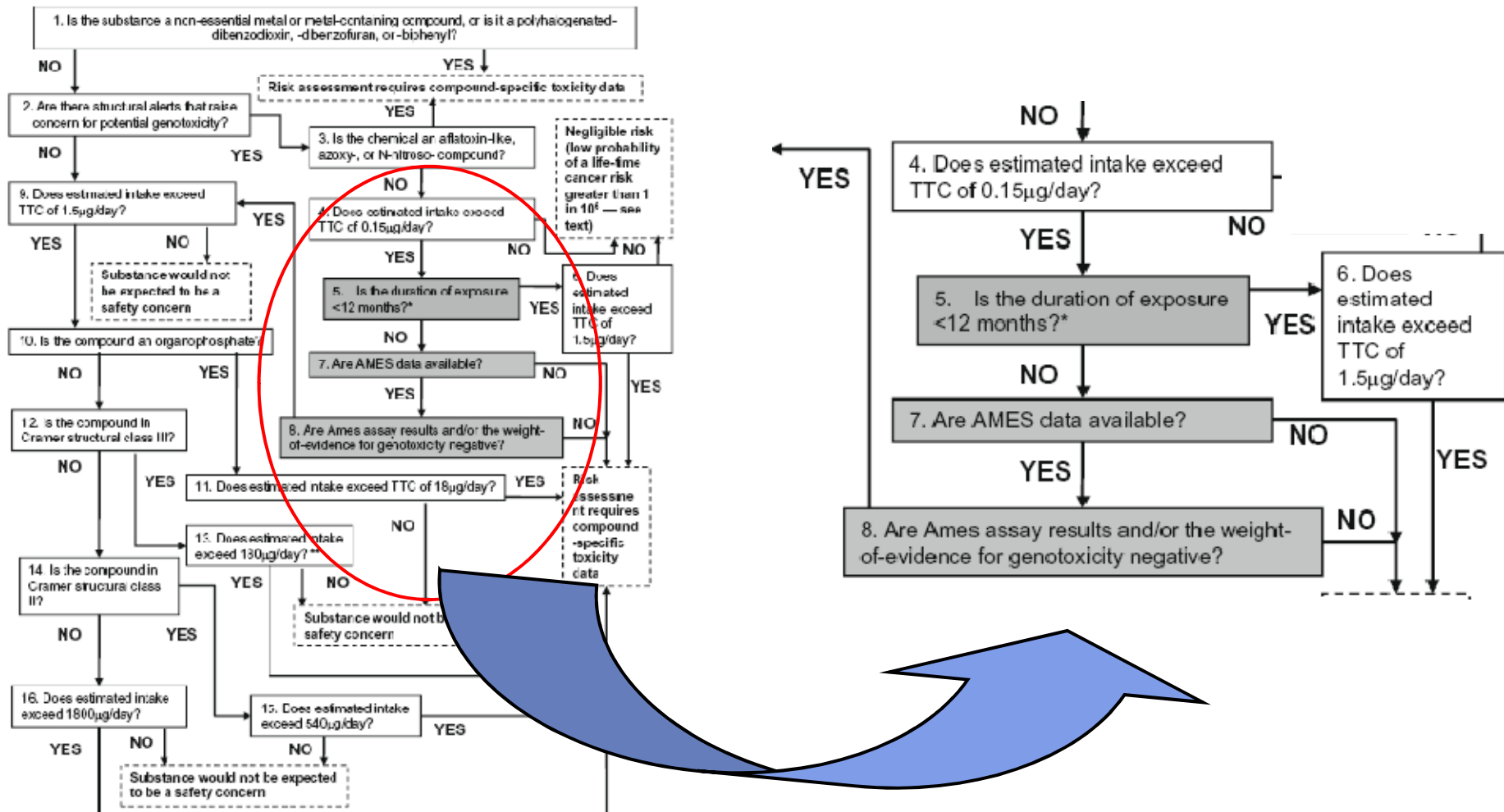
- There is not yet broad international acceptance of this approach for risk assessment, and some questions around early life exposures or dose-rate issues led the ILSI-NA Task Force to recommend a conservative approach until more work is done in this area.
- **Recommendation for now is to use a limit of 1.5 ug/d as the limit for exposures not exceeding 1 year.** It is anticipated that further work may lead to additional refinements.



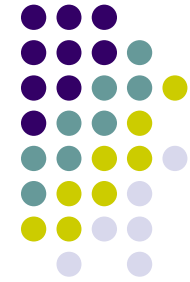
Summarizing

- It is recommended that the TTC limit of 0.15 ug/d for chemicals with structural alerts for genotoxicity be increased to 1.5 ug/d for the following situations:
 - Availability of negative Ames data
 - Exposure not to exceed 1 year

Felter, SP, RW Lane, ME Latulippe, GC Llewellyn, SS Olin, JA Scimeca, TD Trautman. 2009. Refining the Threshold of Toxicological Concern (TTC) for Risk Prioritization for Trace Chemicals in Food. *Fd. Chem. Toxicol.*, 47: 2236-2245.

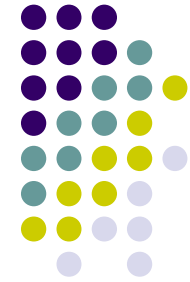


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ILSI-RF Project On Development Of TTC-based Approach For The Evaluation Of Antimicrobial Pesticides: **Steering Team**



- Kirk Arvidson FDA/CFSAN
- Mitch Cheeseman FDA/CFSAN
- Vicki Dellarco US EPA/OPP
- Susan Felter Procter & Gamble
- Tim Leighton US EPA/OPP/AD
- Steve Olin ILSI-RF
- Andrew Renwick University of Southampton
- Troy Seidle Humane Society

Project is being undertaken in collaboration with the U.S. EPA's Office of Pesticide Programs (EPA/OPP) and the American Chemistry Council's Biocides Panel.

ILSI RF: Development of a TTC-based Approach for the Evaluation of Antimicrobial Pesticides



- **Objective:** Develop a framework and/or decision tree incorporating a TTC-based approach as a tool for use in risk assessment of AM pesticides and for addressing higher tier toxicology data requirements for these substances.

Challenges for Using TTC for Antimicrobial Pesticides



- **Chemical Domain**

- The 250+ compounds that are used as AM pesticides span a wide range of chemical classes, including many classes that are not well-represented in the databases underlying existing TTC decision trees.

- **Nature of Toxicity**

- ~ 1/3 of the 250+ compounds are irritants or corrosives but exhibit no significant systemic effects under standard conditions of use.

- **Exposure Considerations**

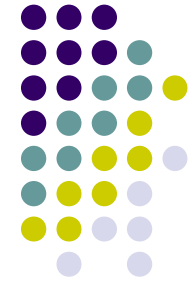
- Dermal and inhalation exposures are common with a number of antimicrobial use patterns,
- Short-term exposure scenarios are the norm for many uses



Project Priorities

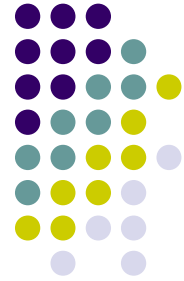
- Priority #1 – Database for Application of TTC to Antimicrobial Pesticides
 - Antimicrobials toxicity data from EPA files being entered in ToxRefDB by EPA/OPP and EPA/ORD
 - Chemical domains for AM TTC being explored
- Priority #2 – Dermal Exposures
 - Developing a tiered screening process for typical antimicrobial exposure scenarios, based on rate of uptake through the skin (Kroes et al., 2007)

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 - **TTC as a tool in mixtures risk assessment**
- ILSI Europe
 - TTC Task Force

HESI-Mixtures Task Force



Rosemary Zaleski (ExxonMobil Biomedical Sciences, Inc.)

Joel Bercu (Eli Lilly)

Alan Boobis (Imperial College, London)

Robert Budinsky (Dow Chemical Company)

Kevin Crofton (USEPA)

Michelle Embry (HESI)

Susan Felter (Procter & Gamble)

Roger Meyerhoff (Eli Lilly)

Gary Mihlan (Bayer CropScience)

Moiz Mumtaz (CDC / ATSDR)

Paul Price (The Dow Chemical Company)

Keith Solomon (University of Guelph)

Linda Teuschler (USEPA)

Raymond Yang (Colorado State University)

Richard Hertzberg (Emory University)

Shanna Collie (Synergy Toxicology)

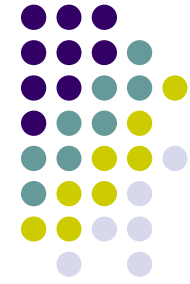
David Kopp (Emory University)

HESI Mixtures Project



- **Objective:** Examine the applicability of TTC to chemical mixtures as a screening-level, prioritization approach
 - Project #1: Synergy: What is the potential for dose or response-additive models to underestimate the toxicity of a mixture at exposure levels of interest?
 - Project #2: Case study using TTC in a mixtures assessment

Project #1: Synergy: Is it an issue when using TTC in the evaluation of a mixture?



- Literature review focused on reports of synergy at (relatively) low doses. However, in most studies, the total dose of mixture components exceeded the NOAEL or benchmark dose for the individual components
- Few studies (6) reported a quantified value for synergy, and there was considerable variation in methodology used
- The maximum potential magnitude of synergy did not exceed ~4-fold in studies meeting the review criteria
- Supports conclusion that toxicological interactions are not likely to occur at the low doses permitted under existing standards for chronic exposure
- Manuscript accepted for publication in Critical Reviews in Toxicology

Project #2: TTC as a Tier 0 Approach for Combined Exposures



- Hypothetical mixture of 10 chemicals detected in US surface water.
- The 10 chemicals fall into various classes, such as fragrances, pesticides, surfactants, personal care products, solvents and petrochemicals.
- Utilizes TTC as a screening-level, Tier 0 approach to help prioritize mixtures of concern
 - Not intended as a quantitative estimate of risk
 - A conservative approach to demonstrate safety (Hazard Index < 1) with a low chance of false negative



Case Study Methodology

- 10 compounds classified into Cramer Classes
- TTC values for each substance assigned
 - Cramer Class I (1800 ug/day = 0.03 mg/kg/day)
 - Cramer Class II (540 ug/day = 0.009 mg/kg/day)
 - Cramer Class III (90 ug/day = 0.0015 mg/kg/day)
- Exposure (mg/kg bw per day) =
Surface water conc (mg/L) \times 0.42 L/day / 18 kg *
- HQ for each substance =
Exposure / TTC value

*Drinking water assumptions made for children to be conservative

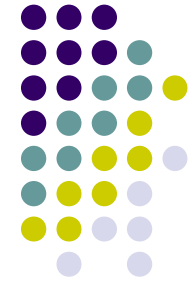
Cmpd	Conc in surface water (µg/L)	Conc in surface water (mg/L)	Exposure (mg/kg / day)	Cramer class	TTC value (mg/kg bw/ day)	Hazard quotient based on TTC
A	1.7	1.7E-03	3.97E-05	I	0.03	1.3E-03
B	0.28	2.8E-04	6.53E-06	I	0.03	2.2E-04
C	1.1	1.1E-03	2.57E-05	I	0.03	8.6E-04
D	0.083	8.3E-05	1.94E-06	II	0.009	2.1E-04
E	3.8	3.8E-03	8.87E-05	II	0.009	9.7E-03
F	34	3.4E-02	7.93E-04	II	0.009	8.7E-02
G	0.076	7.6E-05	1.77E-06	III	0.0015	1.2E-03
H	0.13	1.3E-04	3.03E-06	III	0.0015	2.0E-03
I	0.18	1.8E-04	4.20E-06	III	0.0015	2.8E-03
J	6.1	6.1E-03	1.42E-04	III	0.0015	9.5E-02
Hazard index (sum of hazard quotients)						0.20



Conclusion & Next Steps

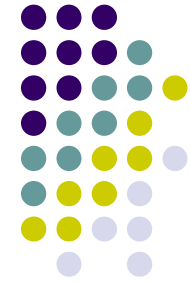
- The calculated hazard index of $0.20 < 1$
- The results of this Tier 0 assessment suggest that advancement to higher assessment tiers is not necessary in this case.
- Next Steps
 - Case study submitted for publication in conjunction with the WHO/IPCS Framework on Combined Exposures (*Critical Reviews in Toxicology*)
 - HESI to co-sponsor mixtures workshop with WHO and ECETOC in February 2011

TTC Projects

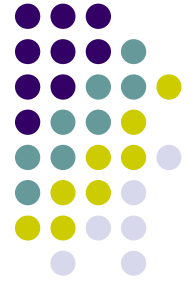


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ILSI Europe: Threshold of Toxicological Concern (TTC) Task Force



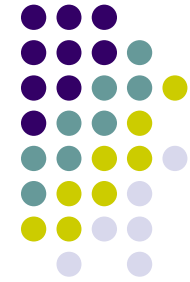
Dr. G. Würtzen –Chair-	Coca-Cola Europe	DK
Dr. D. Carlander*	EFSA	IT
Mr. J. Edwards	DSM Nutritional Products	CH
Dr. S. Felter	Procter & Gamble	US
Dr. H. Hollnagel	Dow Europe	CH
Dr. G. Ouedraogo-Arras	L’Oreal	FR
Prof. em. A. Renwick	University of Southampton	UK
Mr. R. Safford	Unilever	UK
Dr. B. Schilter	Nestlé	CH
Dr. J. Schnabel	Givaudan	CH
Dr. T. Stroheker	Danone	FR
Dr. A. Tritscher	WHO	CH
Ms. T. Wildemann	ILSI Europe	BE



ILSI-EU Projects

- 2009 Continuing Education Course at Eurotox
- TTC for unidentified peaks in food
- International workshop (June 2011) to address scientific challenges of TTC
- Partner in CosMOS project
 - European project co-funded by Colipa and the EC. Goal is to develop tools that can be used to support safety of cosmetic ingredients without the need for animal testing. TTC is one component of this project.

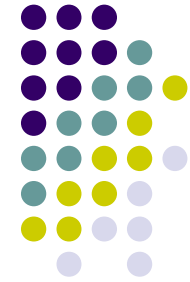
Expert Group on the “Application of the TTC Concept to Unexpected Peaks in Food”



- Aim: to provide guidance to the food industry
- Questions to be answered:
 - How should unknown peaks be handled?
 - Should peaks be entirely analysed or can they be ignored if below a specific threshold?
 - Final revisions to manuscript underway; will be submitted to Food and Chemical Toxicology by end of 2010.

International Workshop

June 2011

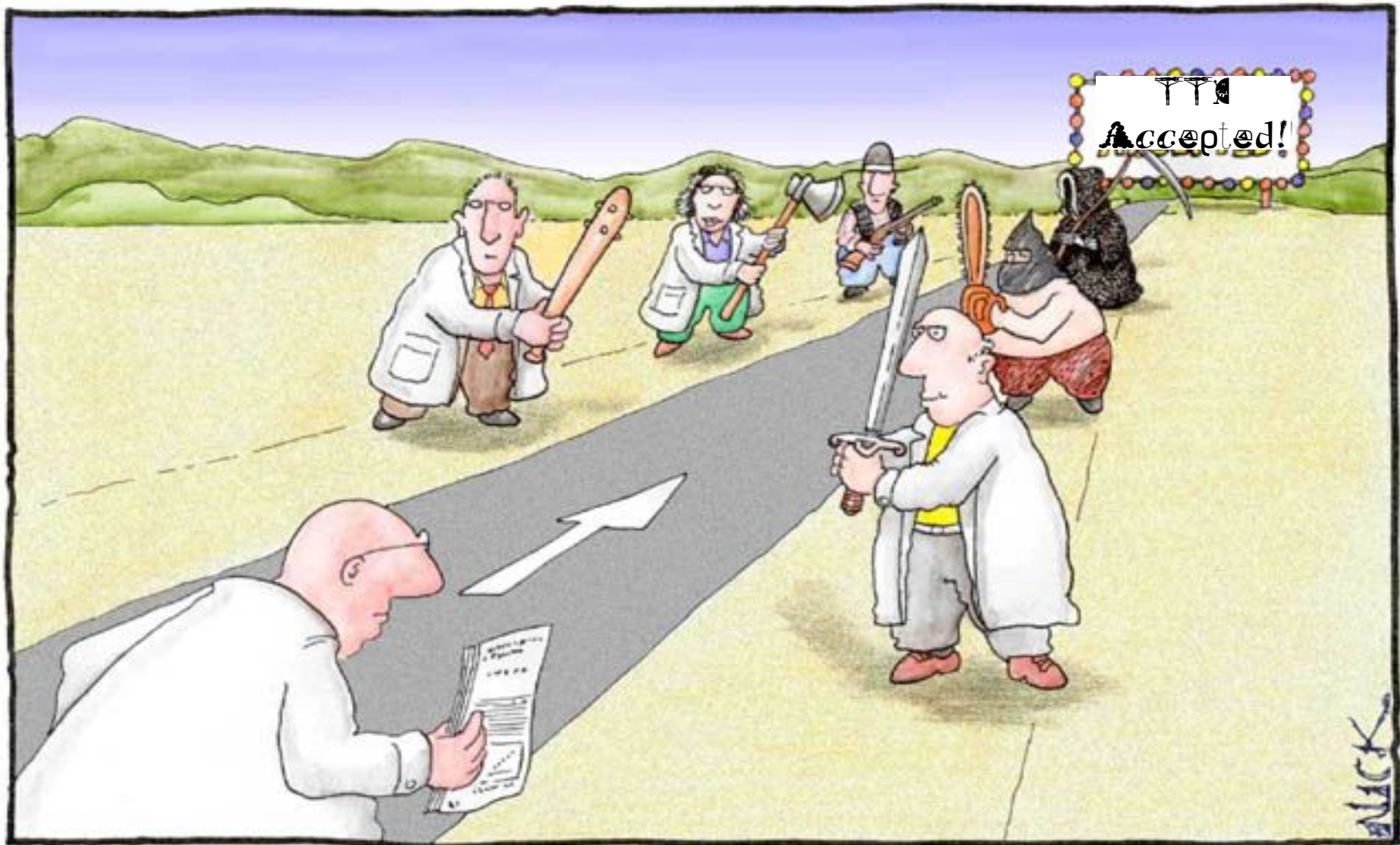


Draft Programme

**Workshop on the
Threshold of Toxicological Concern:
Scientific challenges and approaches**

8 – 10 June 2011
Brussels (Belgium)

- Break-Out Groups
 - Chemical Domain: Cancer
 - Chemical Domain: Noncancer
 - Cancer TTC tier: identification of structural alerts
 - Noncancer: Cramer Classes
 - TTC for non-oral routes of exposure



Most scientists regard TTC as an important, pragmatic tool for the risk assessment of low-level exposures. It is critical to identify concerns and address them so that TTC can enjoy broad international acceptance.