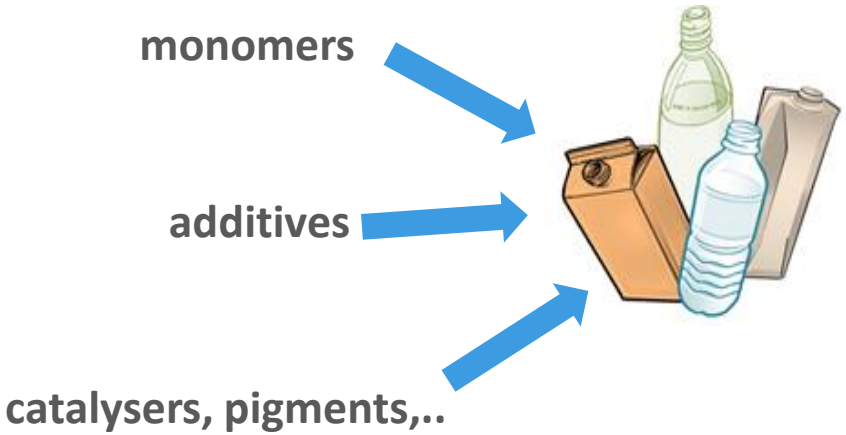
MIGRATOX Project and Adressing NIAS

OFI - Austrian Research Inst. for Chem. and Tech.
FH Campus Wien

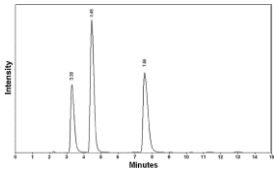
Safety assessment Food Contact Materials

Traditional Focus Safety Assessment:

Which substances are used for the production?



IAS: **I**ntentionally **A**dded **S**ubstances



Chemical analysis!

Safety assessment Food Contact Materials

New focus:

Which substances come out of the packaging?

monomers

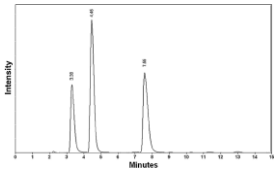
additives

catalysers, pigments,..

IAS: additives, monomers,…

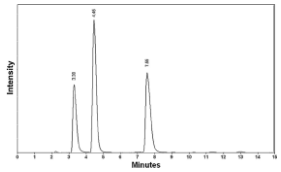
NIAS: degradation products, contaminants, side products

IAS: **I**ntentionally **A**dded **S**ubstances



Chemical analysis!

NIAS: **N**on-**I**ntentionally **A**dded **S**ubstances



Chemical analysis!

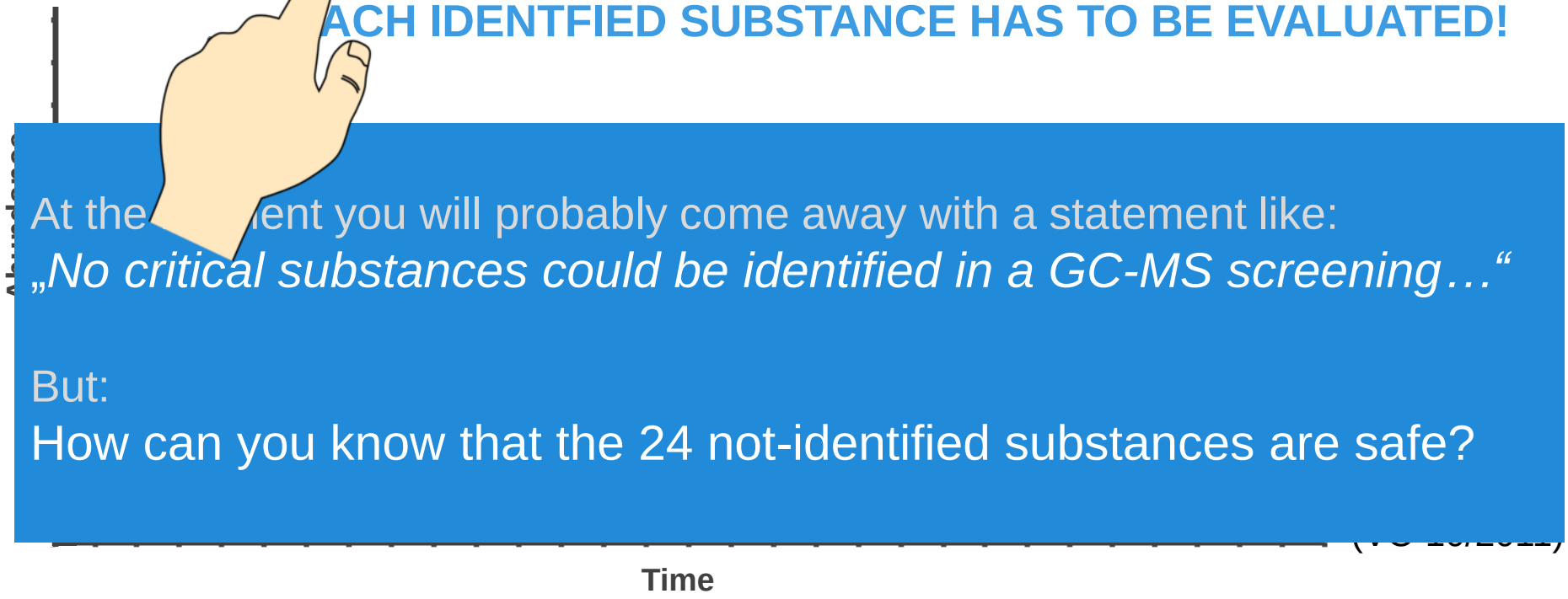
✚ (if necessary)

Bioassays

Example: NIAS Screening (GC-MS):

- 51 detected Peaks in GC Screening
- 24 no clear identification

EACH IDENTFIED SUBSTANCE HAS TO BE EVALUATED!

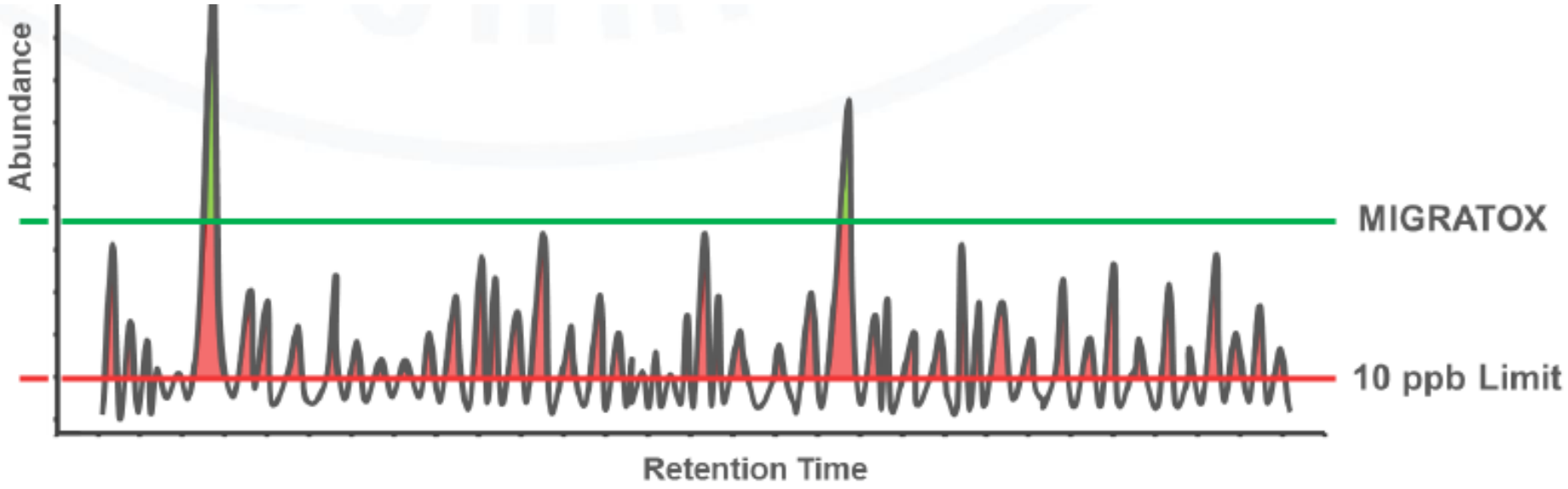


At the moment you will probably come away with a statement like:
„No critical substances could be identified in a GC-MS screening…“

But:
How can you know that the 24 not-identified substances are safe?

At latest since 01.01.2016:
NIAS have to be evaluated according to EU 10/2011:

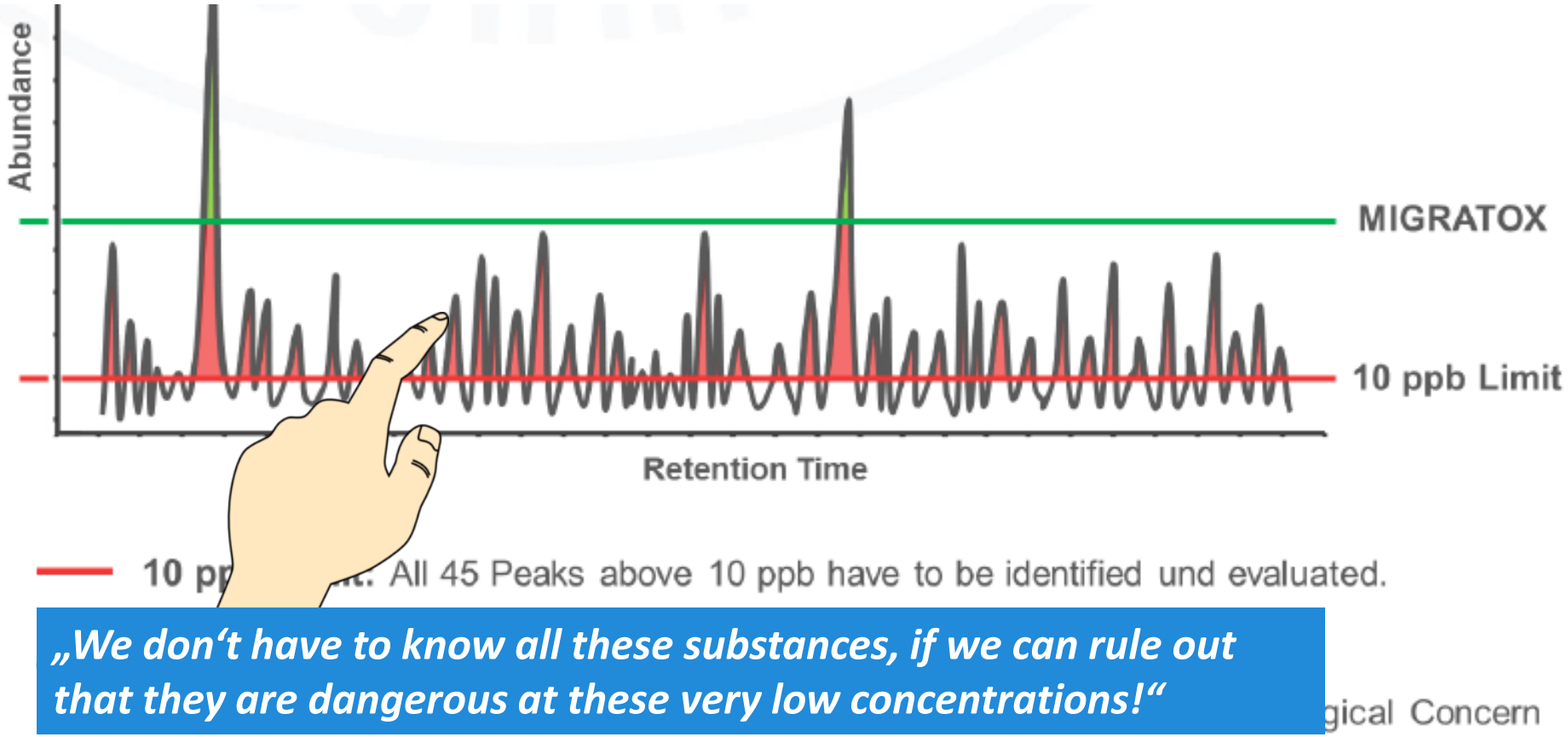
TTC approach for the risk evaluation of NIAS



10 ppb Limit: All 45 Peaks above 10 ppb have to be identified und evaluated.

MIGRATOX : CMR-substances can be excluded by *in-vitro*-tests →
Evaluation only necessary for the 2 Peaks above the Threshold of Toxicological Concern

TTC approach for the risk evaluation of NIAS



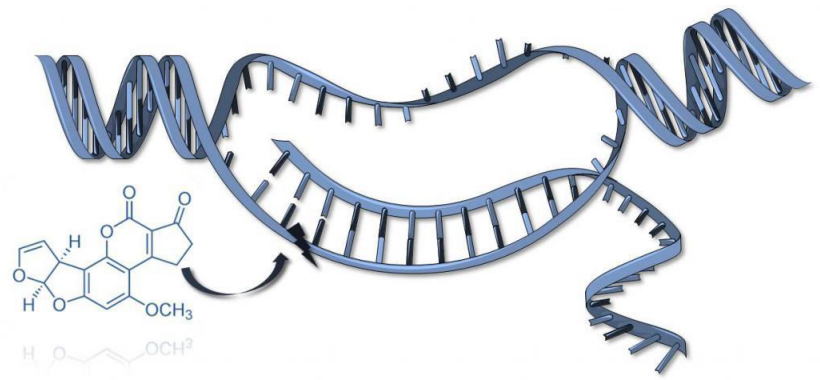
„We don‘t have to know all these substances, if we can rule out that they are dangerous at these very low concentrations!“

Genotox

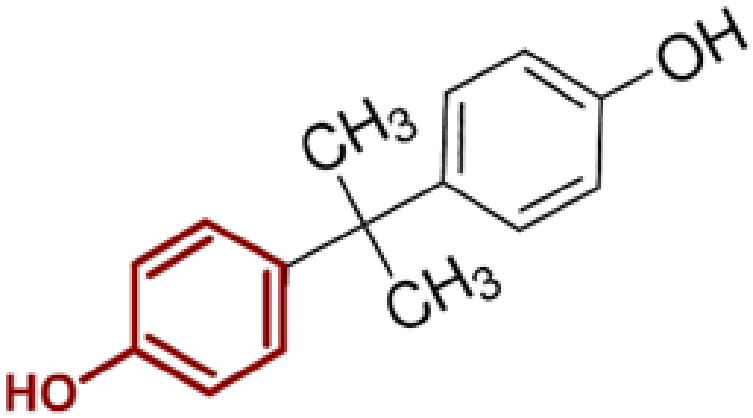
genotoxic…….changes DNA in laboratory test

→ not necessarily mutagenic, cancerogenic in real life!

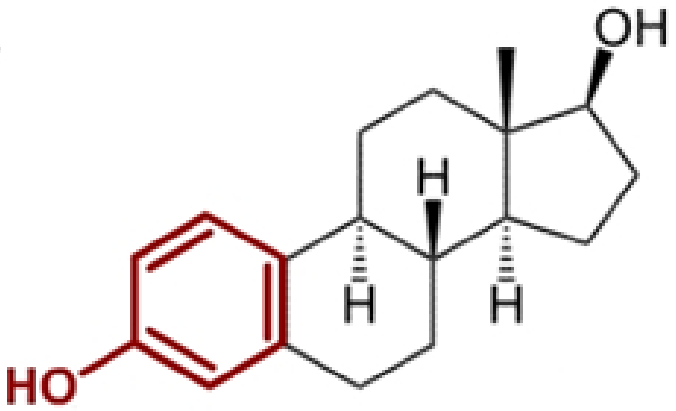
- Potentially harmful at very low doses
- No real safe limits



Endocrine active substances



Bisphenol A
(Monomer of Polycarbonat)



Estrogen (17β-Estradiol)
(Natural female sex hormone)

Harmful at very low doses????

Very controversially discussed

Threshold of toxicological concern (TTC)

unknown substance — **0.15 µg/d → 0.15 µg/L**

Exclude:

- **Genotoxic Substances → *in-vitro Tests***

- PCBs, dioxins → **GC-MS, PAH CALUX**
- heavy metals ✓
- organophosphates → **pesticide screening, argumentation**
- steroids
- endocrine disruptors

} **XENO** ✓

Cramer Class III — **< 90 µg/d → 90 µg/L**

Threshold of toxicological concern (TTC)

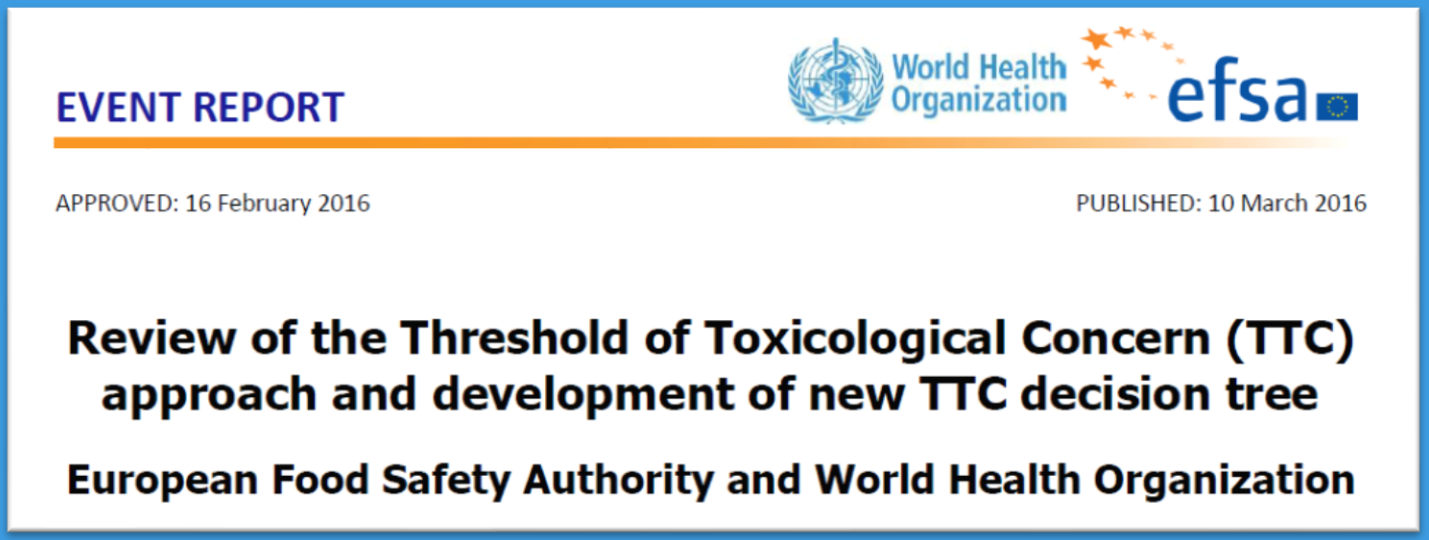
unknow

Exc

- G
- P
- he
- or
- st
- er

EFSA / WHO - Report:

„ …TTC as a tool for the evaluation of mixtures that are not fully characterised [….] if it can also be determined that there are no concerns for genotoxicity, the substance may be placed directly in Cramer Class III…..“



EVENT REPORT

World Health Organization

efsa

APPROVED: 16 February 2016

PUBLISHED: 10 March 2016

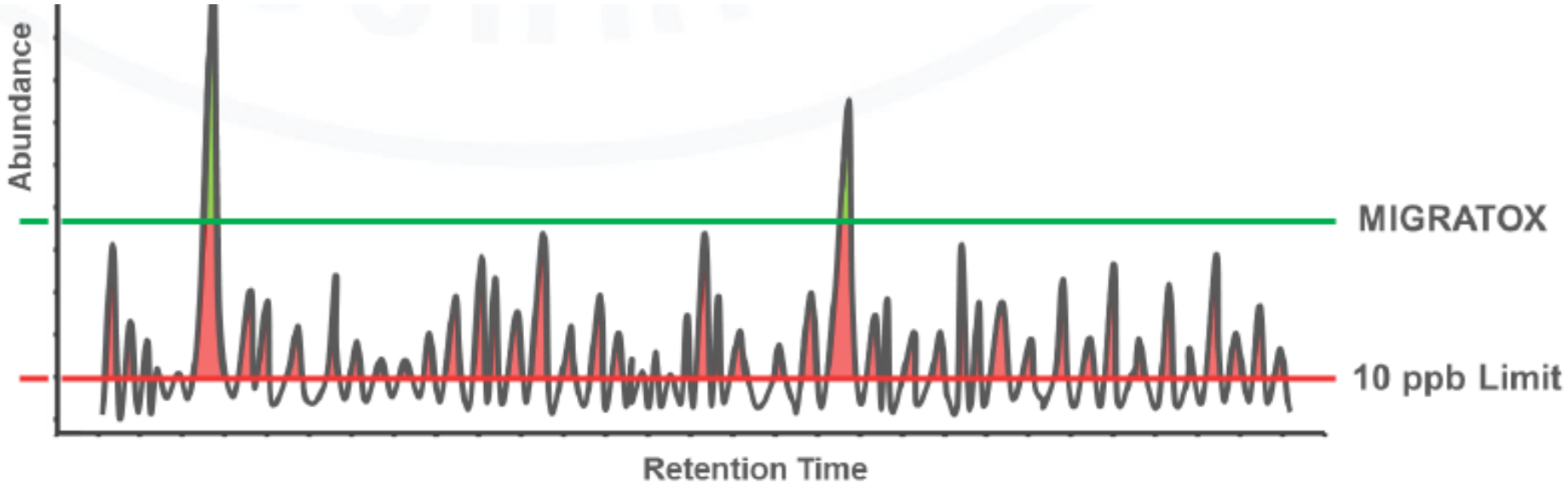
Review of the Threshold of Toxicological Concern (TTC) approach and development of new TTC decision tree

European Food Safety Authority and World Health Organization

Cramer Class III

< 90 µg/d → 90 µg/L

TTC approach for the risk evaluation of NIAS



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Evaluation only necessary for the 2 Peaks above the Threshold of Toxicological Concern

Promising approaches….

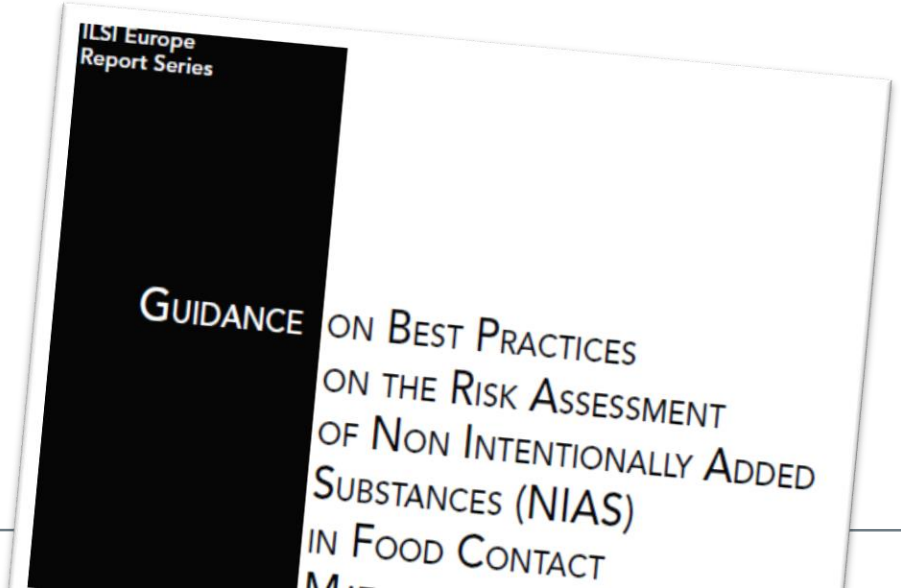
European Parliament
2014-2019

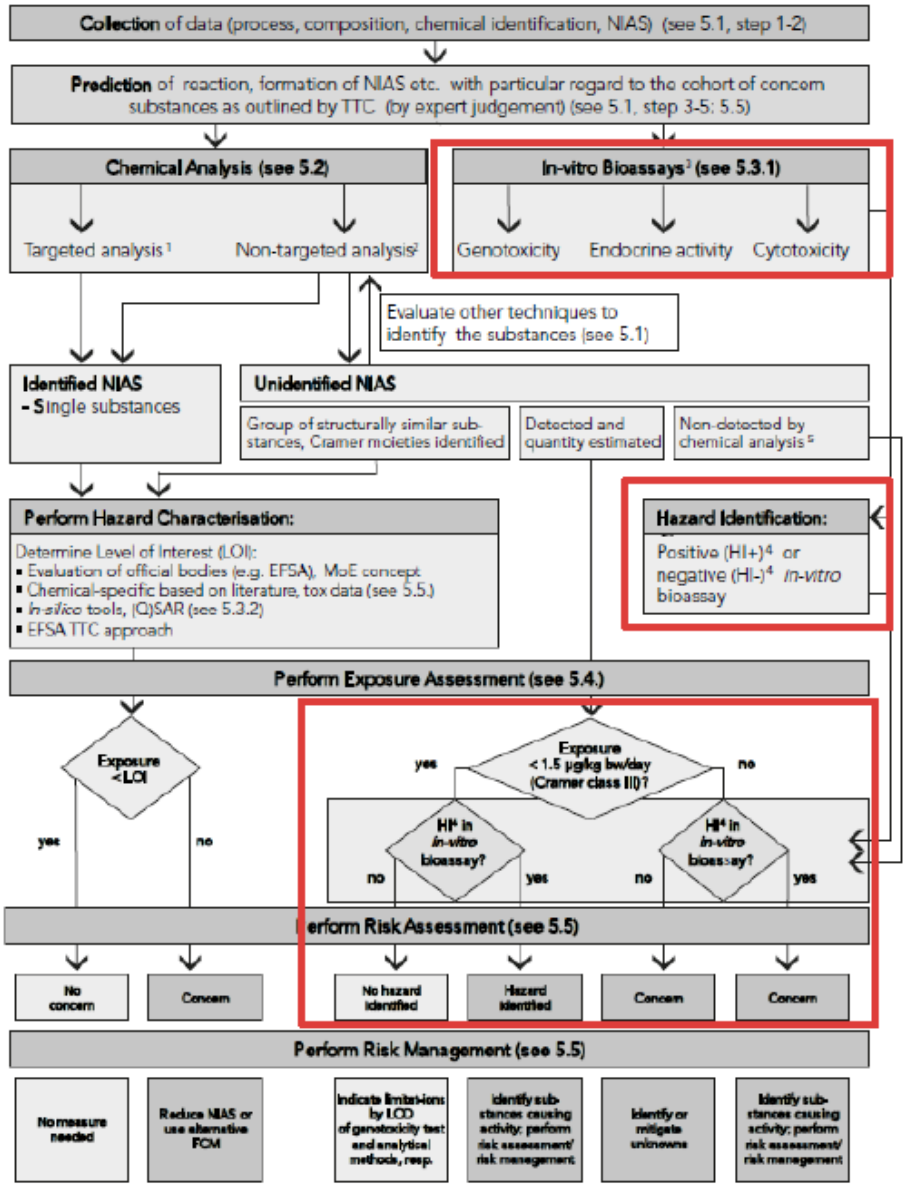
TEXTS ADOPTED

P8_TA(2016)0384

Implementation of the Food Contact Materials Regulation

European Parliament resolution of 6 October 2016 on the implementation of the Food Contact Materials Regulation (EC) No 1935/2004 (2015/2259(INI))

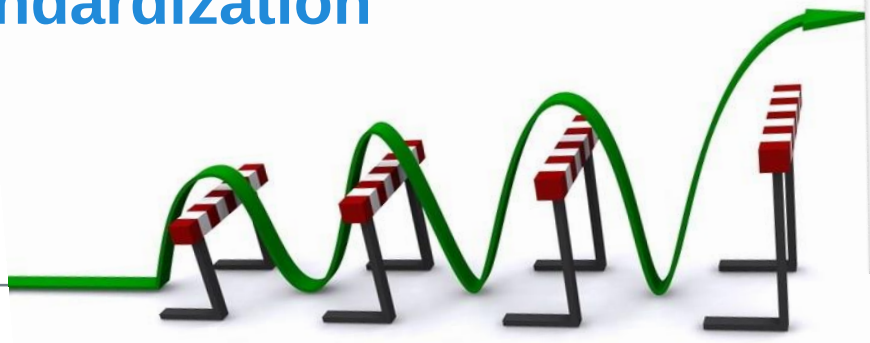


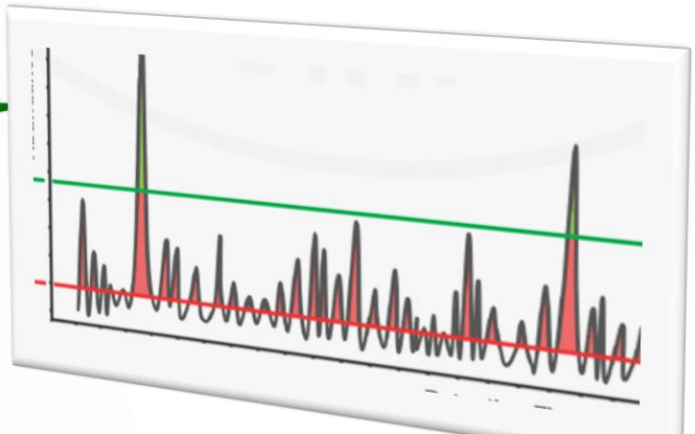


Promising approaches – but still a lot of work to do

But genotoxic substances can already be harmful at these very low concentrations!

- **Sensitivity:** many genotox assays are not sensitive enough to detect low concentrations of genotoxins
- **Sample preparation:** false negatives (e.g. loss of volatiles), false positives (contaminants)
- **Validation:** e.g. influence sample matrice
- **Standardization**





Genotoxicity testing for medical devices / FCM additives

Regulatory testing of medical devices and new FCM additives:

- AMES Test (Bacterial Reverse Mutation)
-
- Mammalian cell micronucleus test

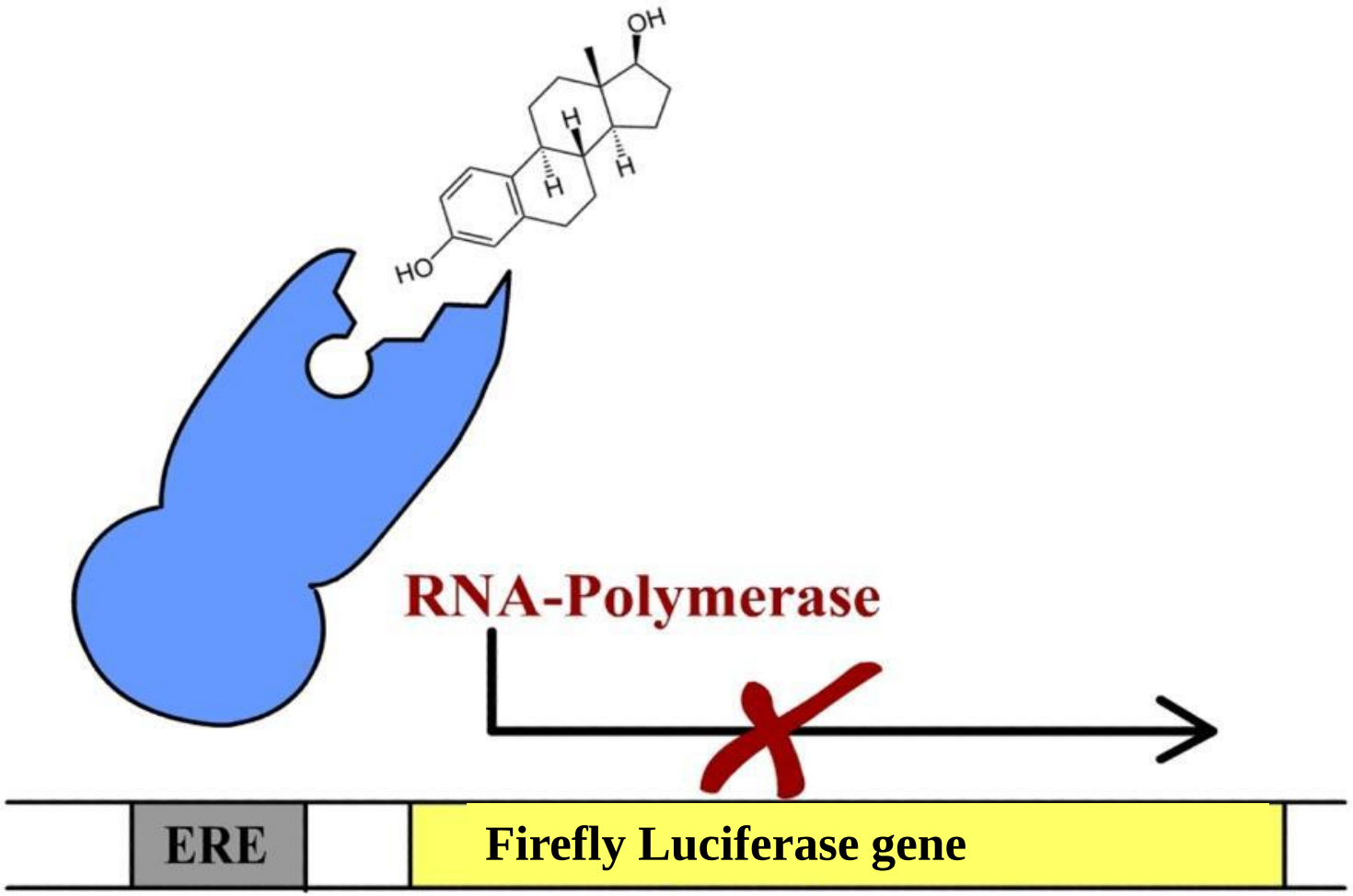
Genotoxicity testing for medical devices / FCM additives

Regulatory testing of medical devices and new FCM additives:

- AMES Test (Bacterial Reverse Mutation) approx. 4.000 €
- Mammalian cell micronucleus test approx. 11.000 €

- **High limits of detection**
- **Many false positives**
- **High costs**
- **Not absolutely necessary for TTC-approach**

Example: Function of a Bioassay



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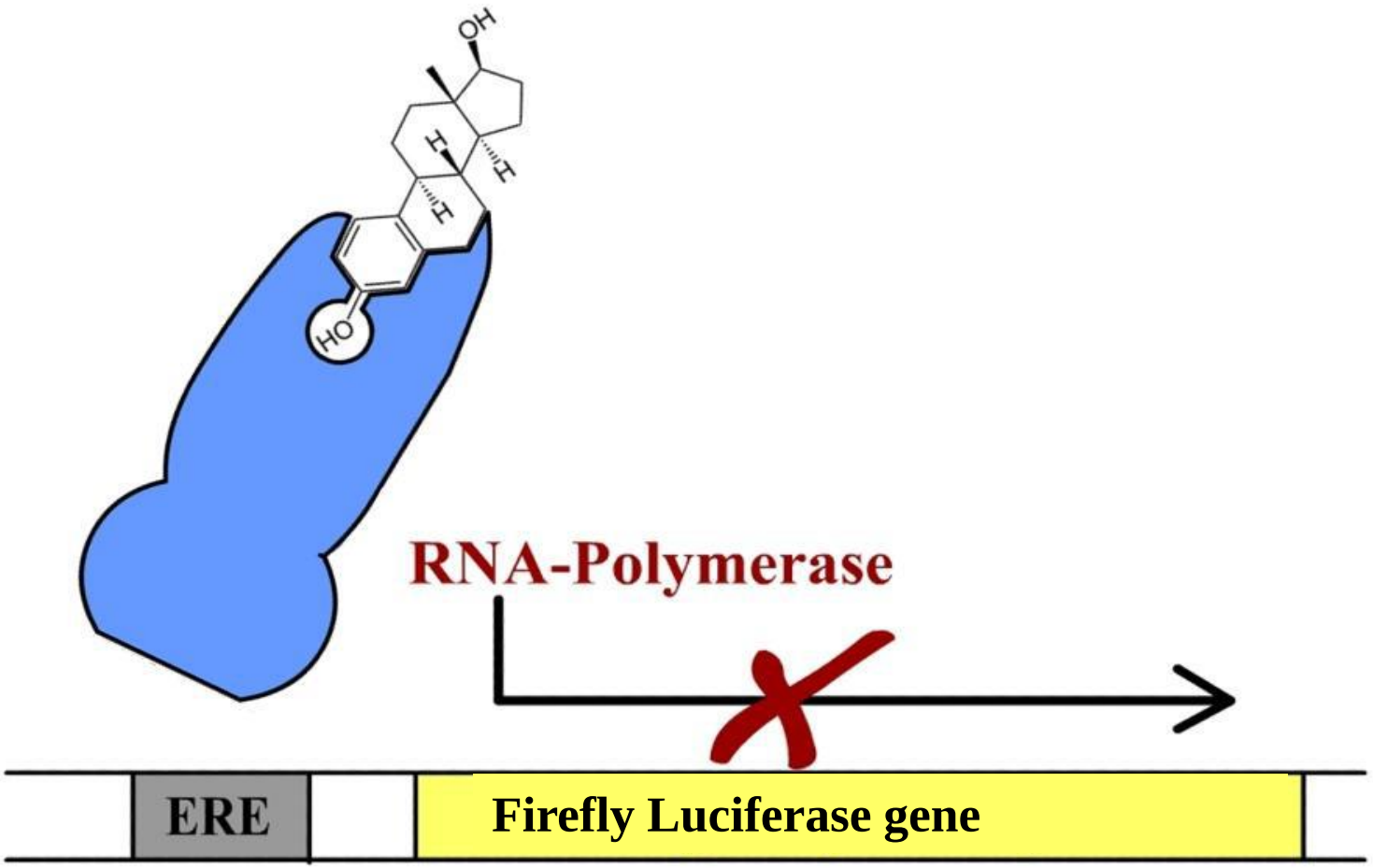

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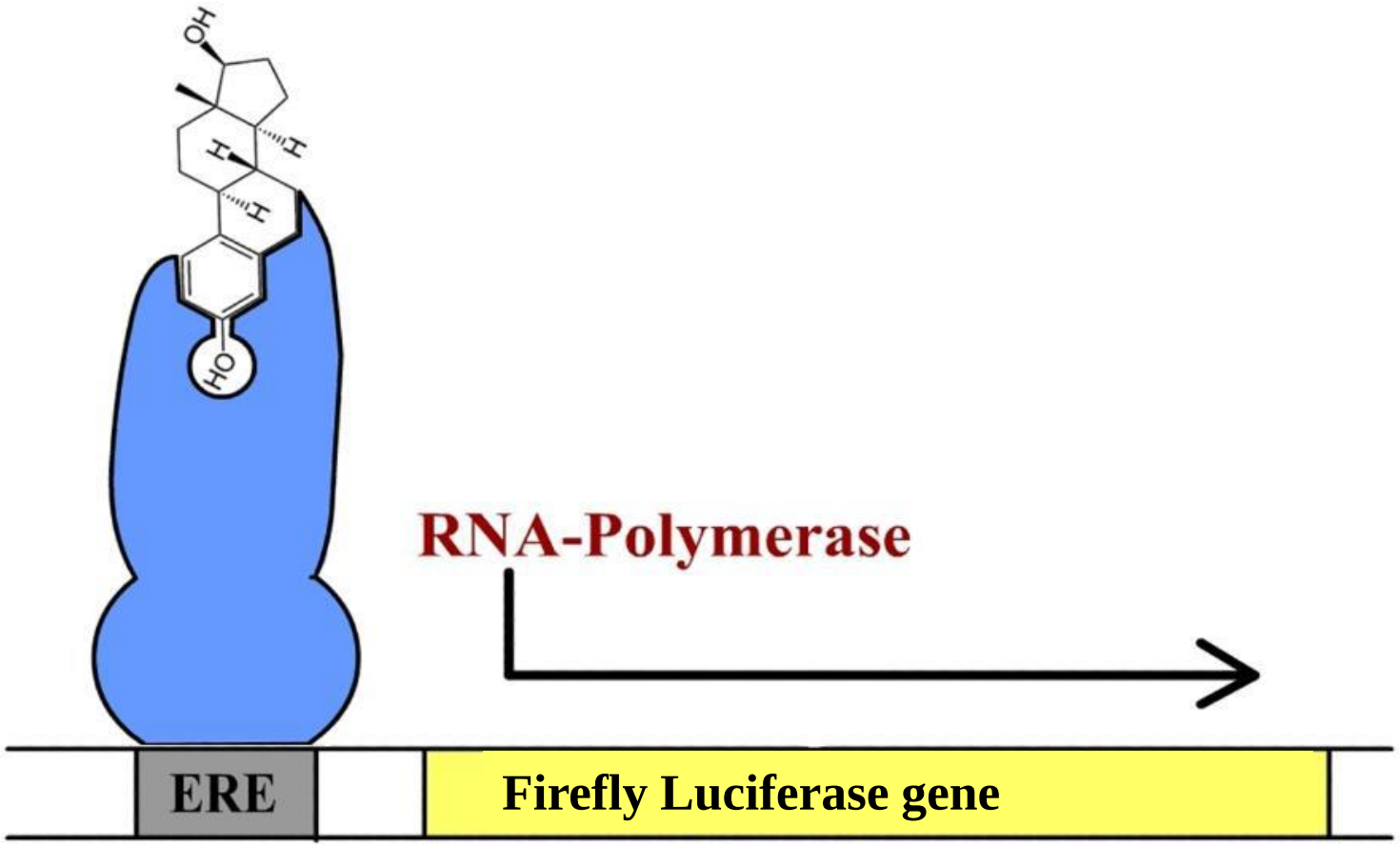

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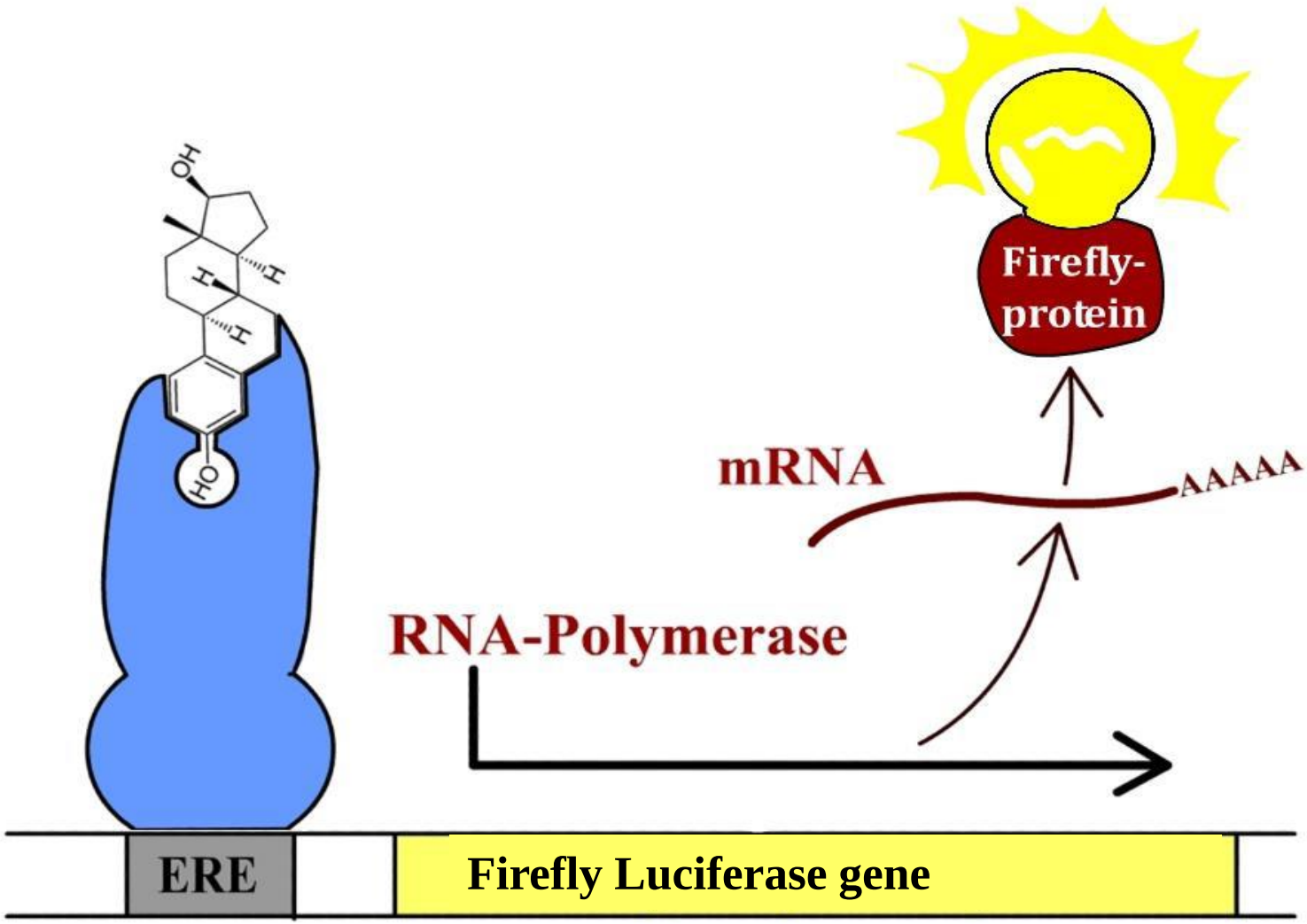

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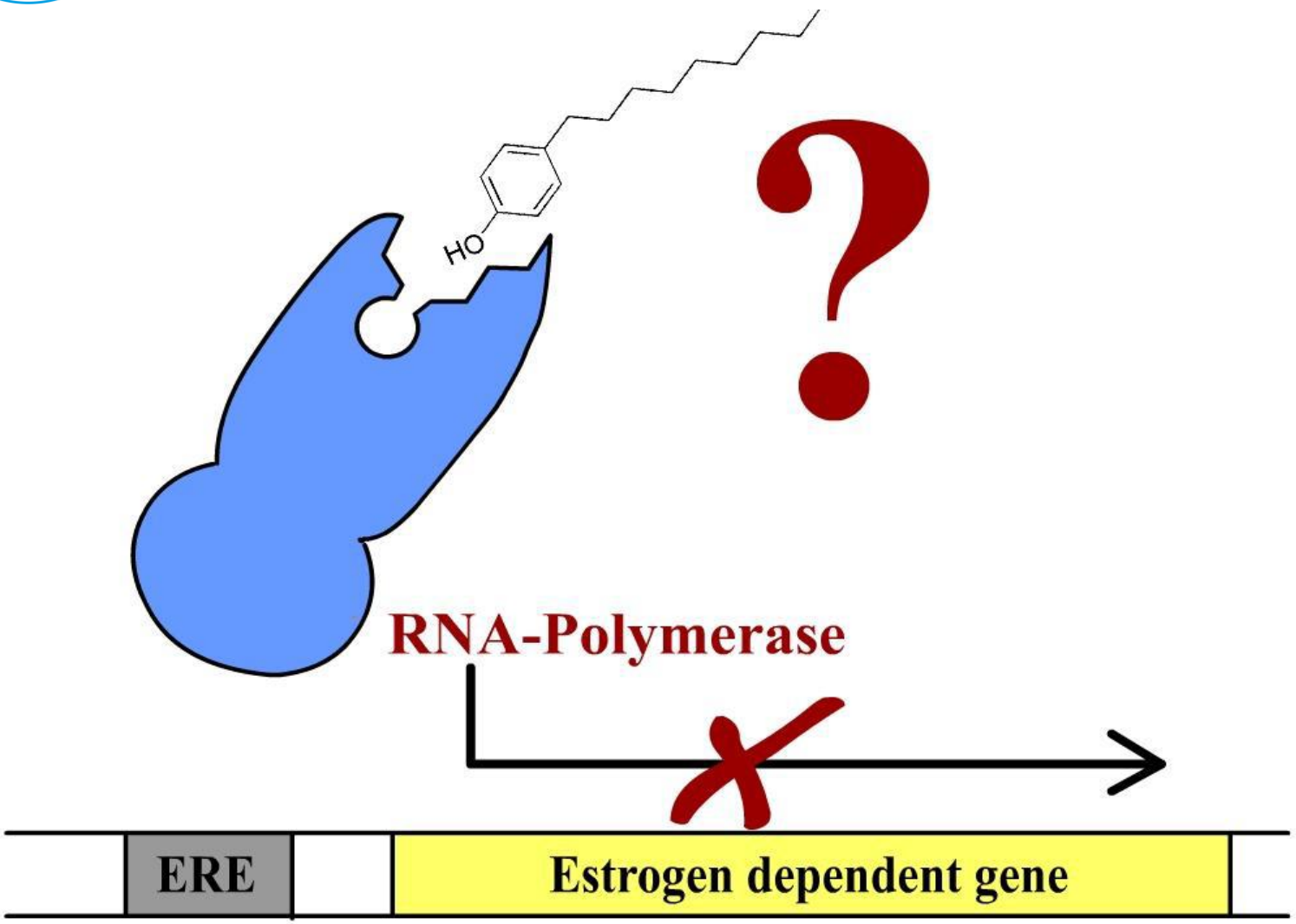
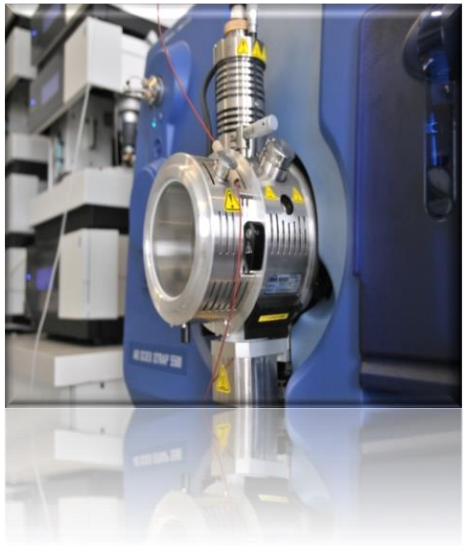


Chemical Analysis

HPLC-UV/VIS-MS/MS3

Dionex U3000
Qtrap 5500, Triple-Quad with linear Ion trap
Source: ESI and APCI

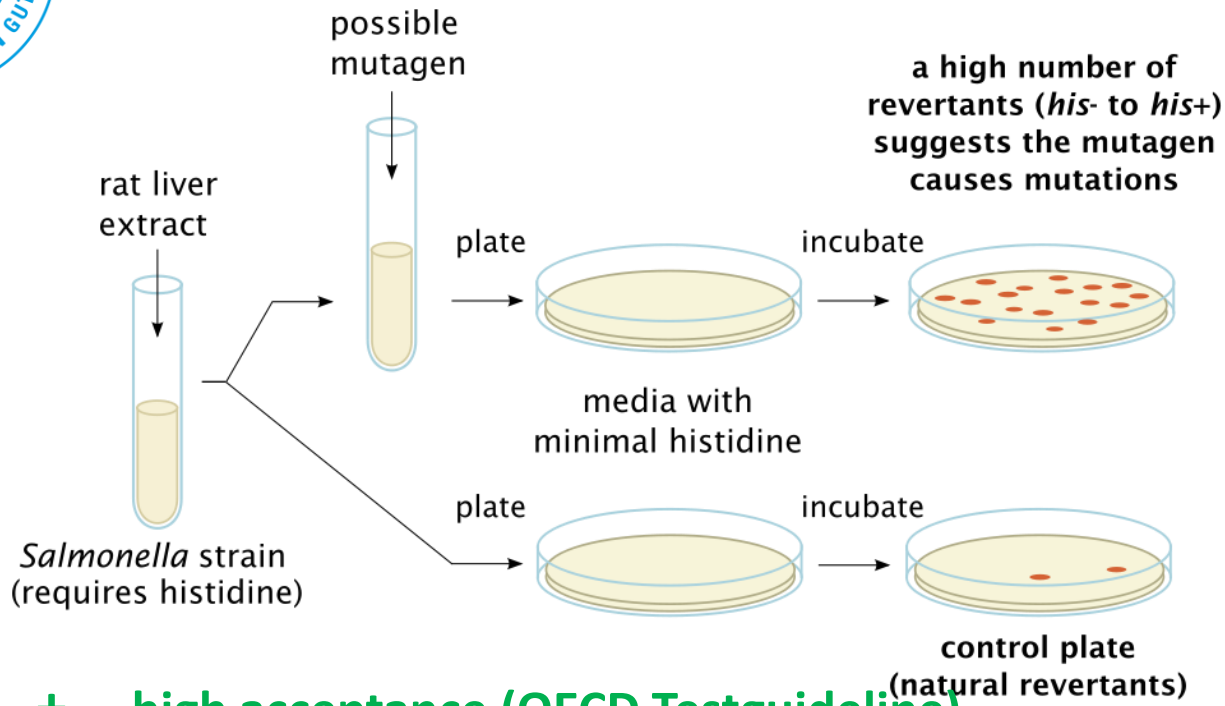


GC MS

- TDU-GC/MS: 7890A (GC) + 5975C inert (MS) + FID with multipurpose Sampler: TDU/HS/FI
- Screening of unknown substances + Semi-quantification with FID

Limit of detection: < 10 ppb

AMES Test



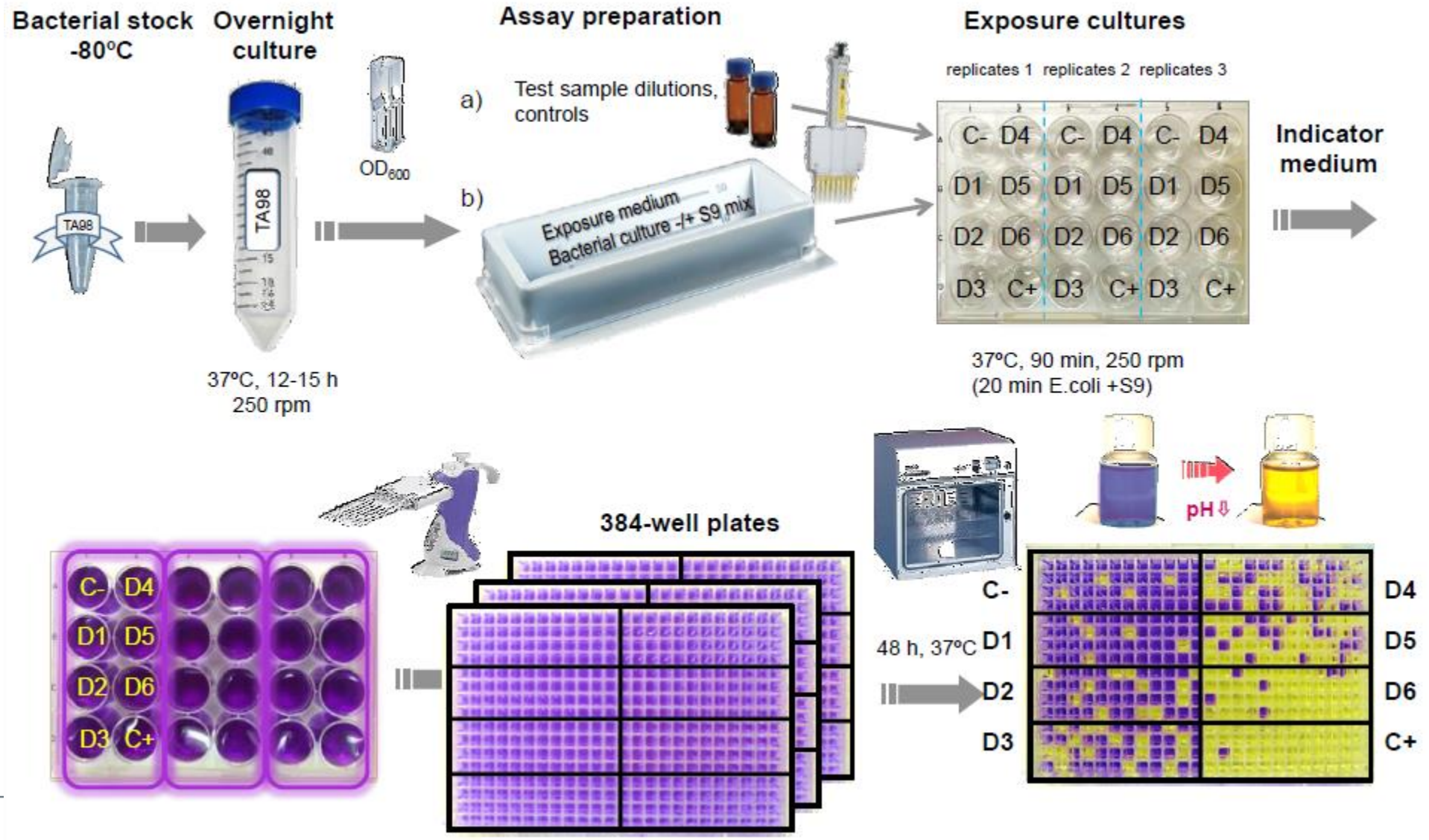
\+ high acceptance (OECD Testguideline)

\+ easy inclusion of metabolism

\+ Focus on relevant (directly DNA-active) gentoxins

\- Bacteria instead of human cells
  - false positives
  - false negatives (only point/frameshift mutations)

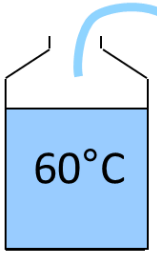
Miniaturized AMES test



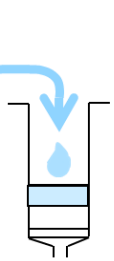
Planned working steps

- Sensitivity:
  - comparison of *in-vitro* methods / sample preparations
  - representative test substances for comparing sensitivity
- Sample screenings
  - How many positives? → Focus on avoiding false-negatives, or on avoiding false-positives?
- Sample preparation:
  - Comparison of sample preparation methods
  - Validation: loss of volatiles, contaminations,..
- Validation:
  - Ensure that methods are suitable for FCM migrates/extracts
- Standardization
  - Defined protocols, specific guidelines
  - Acceptance by cooperation with authorities

Validated analysis strategy

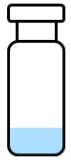


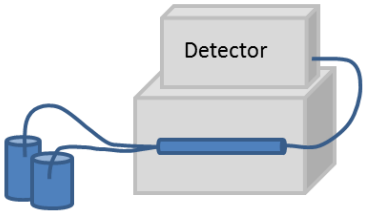
Migration according to (EU) 10/2011



Concentration step (Evaporation or SPE)

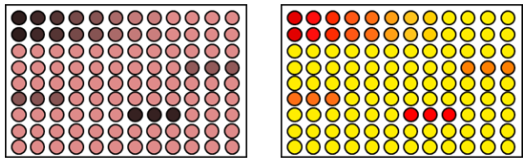
Transfer to DMSO



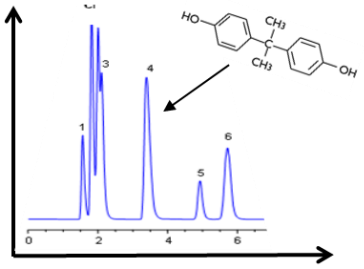


Chemical trace analysis
GC-MS/FID, HPLC-MS³

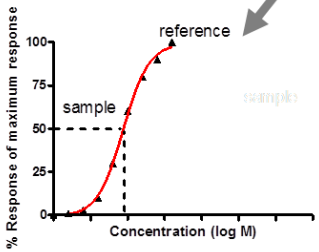
S9 Rat liver extract



Bioassays
(with and without simulated metabolism)



Identification of DNA-active compounds



Comparison to activity of reference standards

FCM Industry knows Bioassays mainly from scandals

Scientists Fear Chemical in Plastic Could Be Harmful

abc NEWS

By JAIME J. HENNESSEY
July 6, 2006

From food-storage containers to disposable silverware, plast
are such a part of our lives that it's
that could harm u

BBC NEWS

derStandard.at › Gesundheit › Leben › Umweltmedizin

Inland Wirtschaft Web Sport Panorama Etat

Weichmacher

Österreich verhält
Bisphenol A in Ba
stecken aber noc

Österreichische K
Substanzen meh
2011 will Gesun
Massenchemika
in "kindernahen
verbieten. Zu fi
Beschichtung
Trinkflaschen

foto: ernst rose/pixelio.de

Plastic chemicals 'feminise boys'

Chemicals in plastics alter the brains of baby boys, making them "more feminine", say US researchers.

Males exposed to high doses in the womb went on to be less likely to play with boys' toys like cars or to join in rough and tumble games, they found.

Male hormones drive boyish play

The University of Rochester team's latest work adds to concerns about the safety of phthalates, found in vinyl flooring and PVC sho

The findings are reported in the In

What's in YOUR blood?

First Run Features presents A DOCUMENTARY BY WERNER BOOTE

PLASTIC PLANET

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News > Science

Study shows dangers of BPA chemical used in plastic packaging

Bisphenol A is used to line drinks cans and in tests affected the way genes work in the brains of laboratory rats

Are Plastic Baby Bottles Harmful?

By Laura Blue | Friday, Feb. 08, 2008

If a new report is to be believed, an entire generation of children has grown up drinking a toxic chemical from their earliest months: bisphenol A. A consortium of North American environmental and health groups released a paper Thursday showing that many major-brand baby bottles leach bisphenol A, and is now calling for a moratorium on the use of the compound — used to make polycarbonate plastic

Research Project MigraTox

Be part of our Industry Board!

Advantages for Project members:

- Regular Project Meetings to **get informed about new developments**
  - Update on new developments, Expert presentations
  - **Presentation of project results**

- Don’t let yourself surprise, better be part of these new developments!

- **Analysis of own samples** with *in-vitro* bioassays
  - **Early warning** in case of positive samples
  - Demonstrate that everything is done to ensure safety

„Safety by Design“: Application Bioassays

	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	Sample 6
Estrogen	++	-	-	-	-	++
Anti-Estrogen	-	-	-	-	-	-
Androgen	-	-	-	-	-	-
Anti-Androgen	+	-	-	-	-	-
Cytotox	-	-	+	-	-	+++
Genotox	-	-	-	-	-	+

Vielen Dank an das Team !


Dr. M. Pyerin


Dr. N. Reischütz


Dr. C. Kirchnawy


DI C. Hartl


R. Razlozhka, BSc


Dr. J. Mertl, MBA


Dr. M. Washuettl

Und an unsere Forschungspartner:

AGES

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Mitglied bei: ACR AUSTRIAN COOPERATIVE RESEARCH

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