



Ministerie van Volksgezondheid,
Welzijn en Sport

SenterNovem
Agentschap voor duurzaamheid en innovatie

ASAT Innovation Programme

The potential of genomics technologies Technology enabling ASAT

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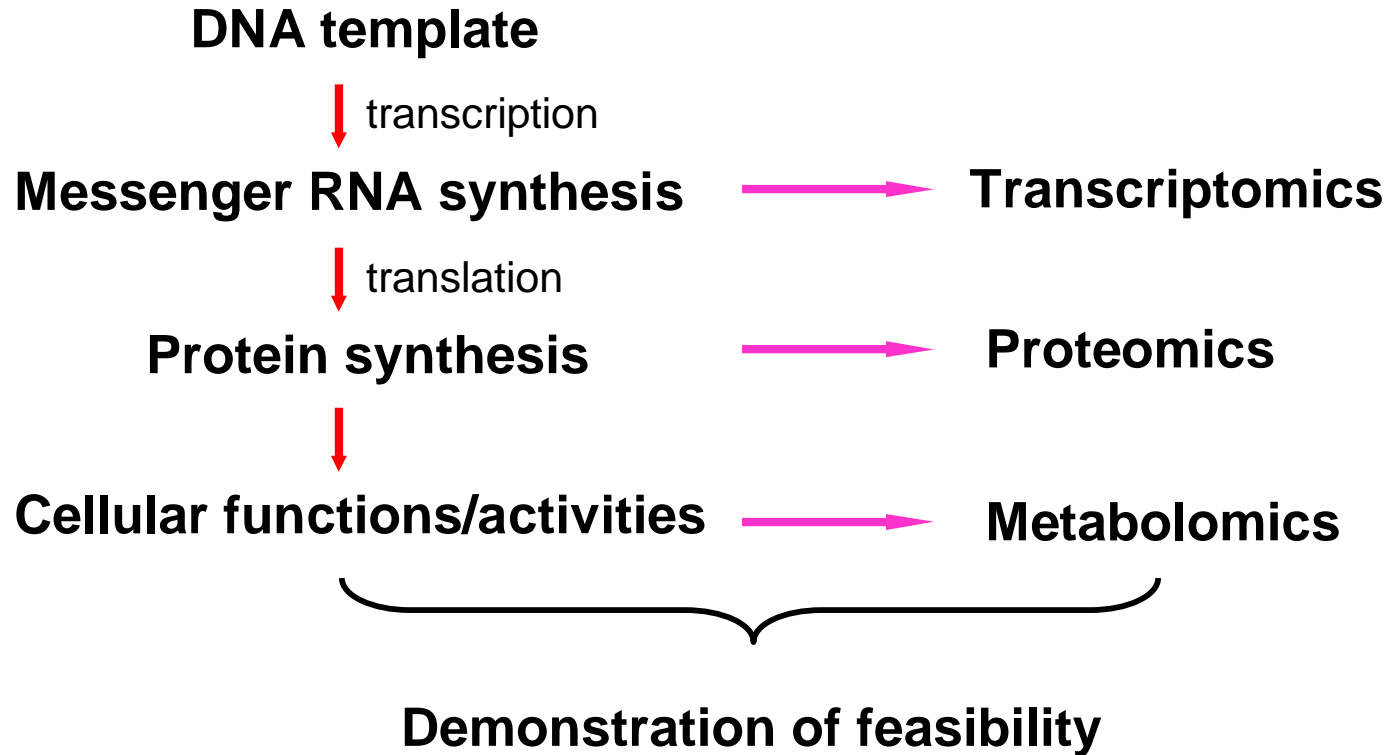


Netherlands 
Toxicogenomics | CENTRE

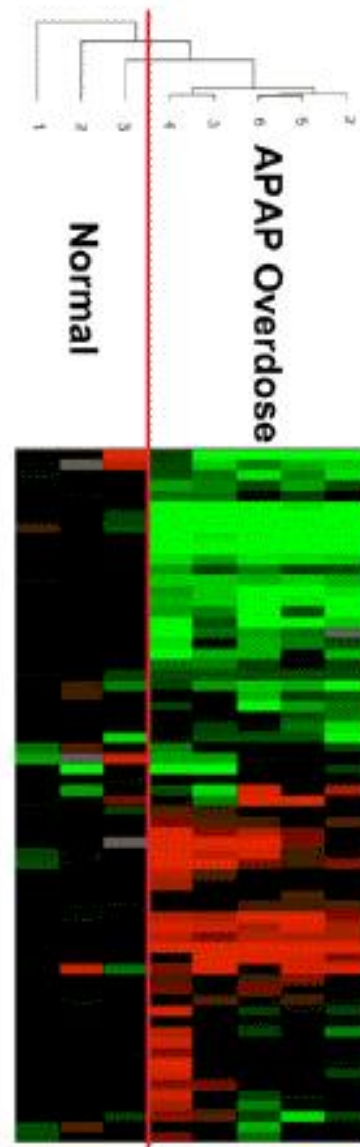
Why are 'omics technologies relevant for ASAT ?

- For providing a better scientific basis for chemical risk assessment in humans.
- For providing relevant data on toxic responses in humans at “daily life” exposure levels, e.g. at rather low dose.

Currently available 'omics technologies for ASAT purposes

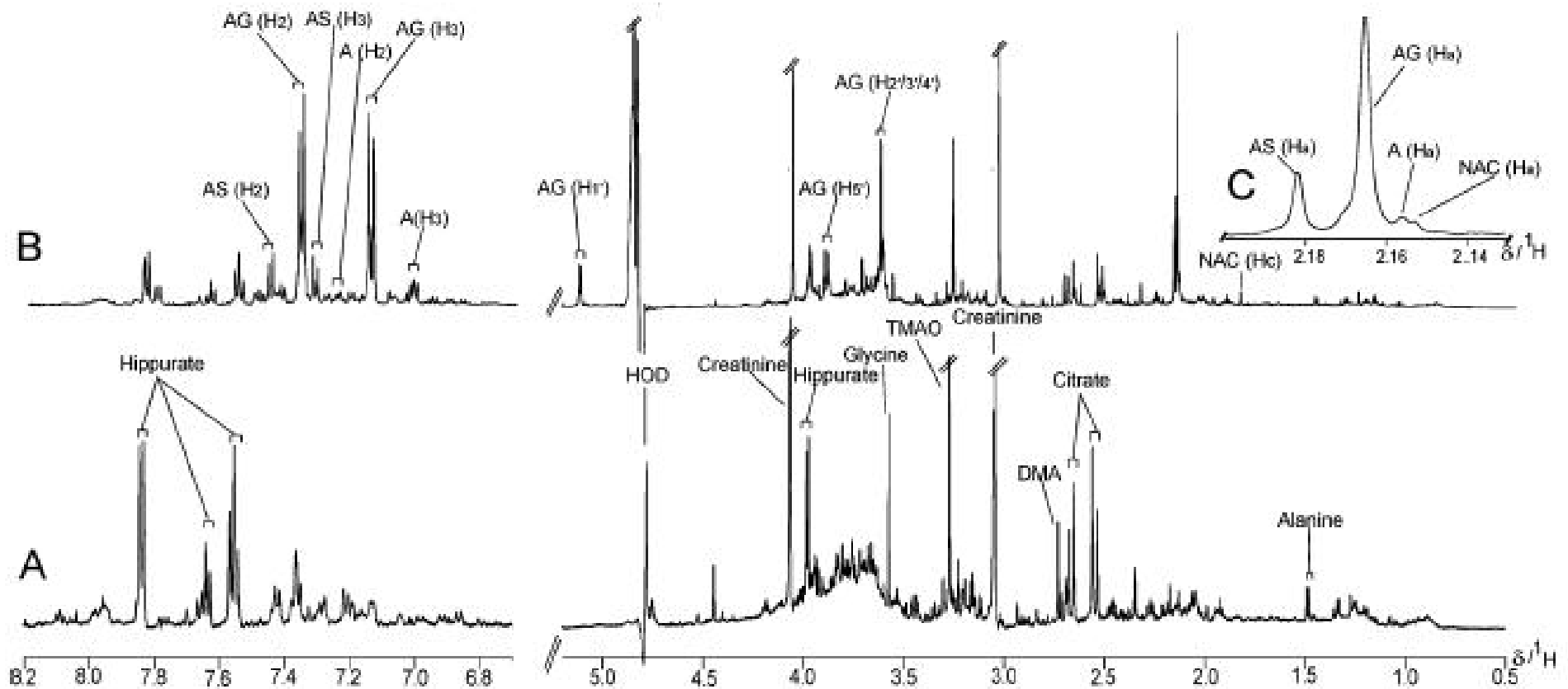


Transcriptomics of paracetamol



Applying a human orthologue (66 genes) of a 270 rat blood gene predictor for hepatotoxicity to blood from acetaminophen overdose victims versus controls allows clear separation

Metabolomics of paracetamol



Typical ^1H NMR spectra of urine from participants: (A) no analgesic intake; (B) after ingestion of an unknown dose of acetaminophen; (C) expansion on acetaminophen region at $\delta \approx 2.16$
Holmes et al, Anal. Chem. 2007

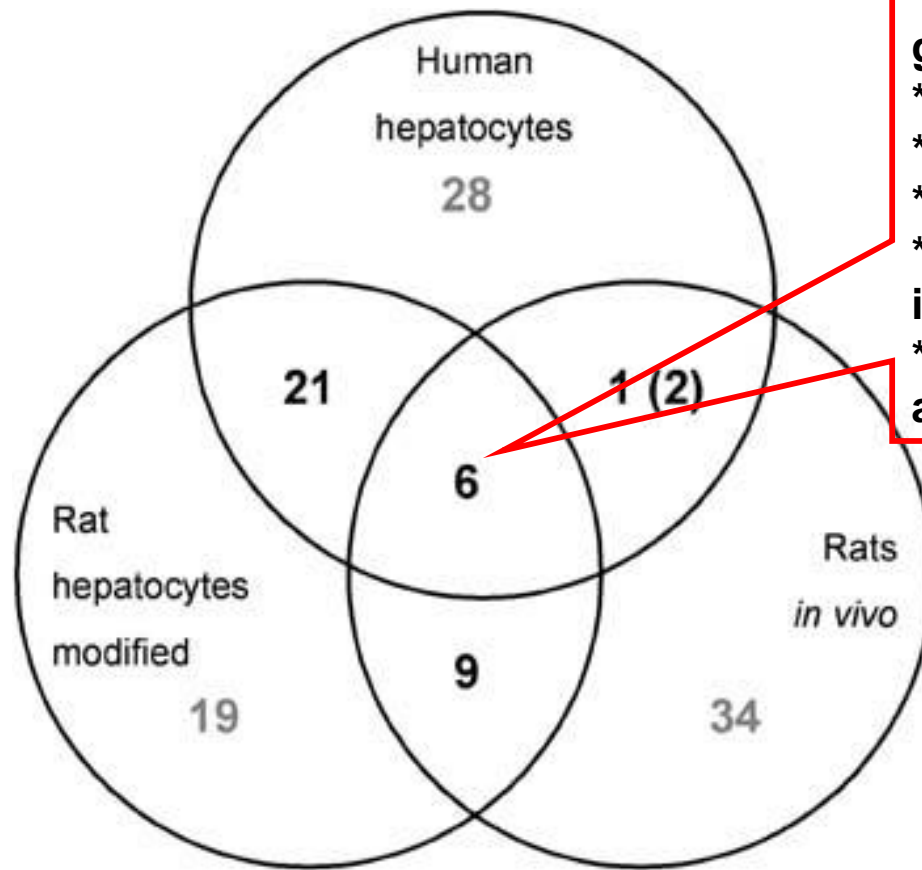
First aim of this project

- To deliver a demonstration system on genomics technologies for the purpose of human safety assessment
- Through applying 'omics technologies to a case study on human volunteers
- By explicitly exploring the low dose range

How will this contribute to developing alternatives to animal toxicity models ?

- Alternative *in vitro* models should predict *in vivo* effects in humans.
- Rodent liver models are frequently used as an *in vitro* alternative in pharmacological, toxicological and metabolic studies
- The use of human hepatocytes is preferential in order to predict *in vivo* responses in humans
- The human liver *in vitro* model needs to be biologically validated in intact humans, in order to demonstrate its relevance for the situation *in vivo*

Paracetamol-induced pathway changes in rat in vivo/in vitro vs human in vitro



- * metabolism in general
- * lipid metabolism
- * fatty acid metabolism
- * electron transport
- * processes occurring in peroxisomes
- * metabolism of amino acids

A. Kienhuis, M. van de Poll, H. Wortelboer, M. van Herwijnen, R. Gottschalk, A. Boorsma, J. Kleinjans, R. Stierum, C. DeJong, J. van Delft.
Inter-species and in vitro – in vivo comparison of acetaminophen-induced gene expression profiles. ToxSci 2008, in press

Second aim of this project

- To explore *in vitro/in vivo* extrapolations of 'omics responses to paracetamol in humans
- Thus validating already developed human liver models *in vitro*
- Thereby increasing the acceptance of human *in vitro* models for assuring chemical safety by relevant stakeholders.

Collaborations

- Within the Netherlands Toxicogenomics Center:
 - Maastricht University
 - RIKILT Institute of Food Safety
 - TNO Quality of Life
- With industry:
 - Center for Drug Safety Sciences
The Hamner Institute for Health Sciences
North Carolina, US