



Volatile analyses from humans: the future diagnostic

An investigation of volatile compounds
associated with disease

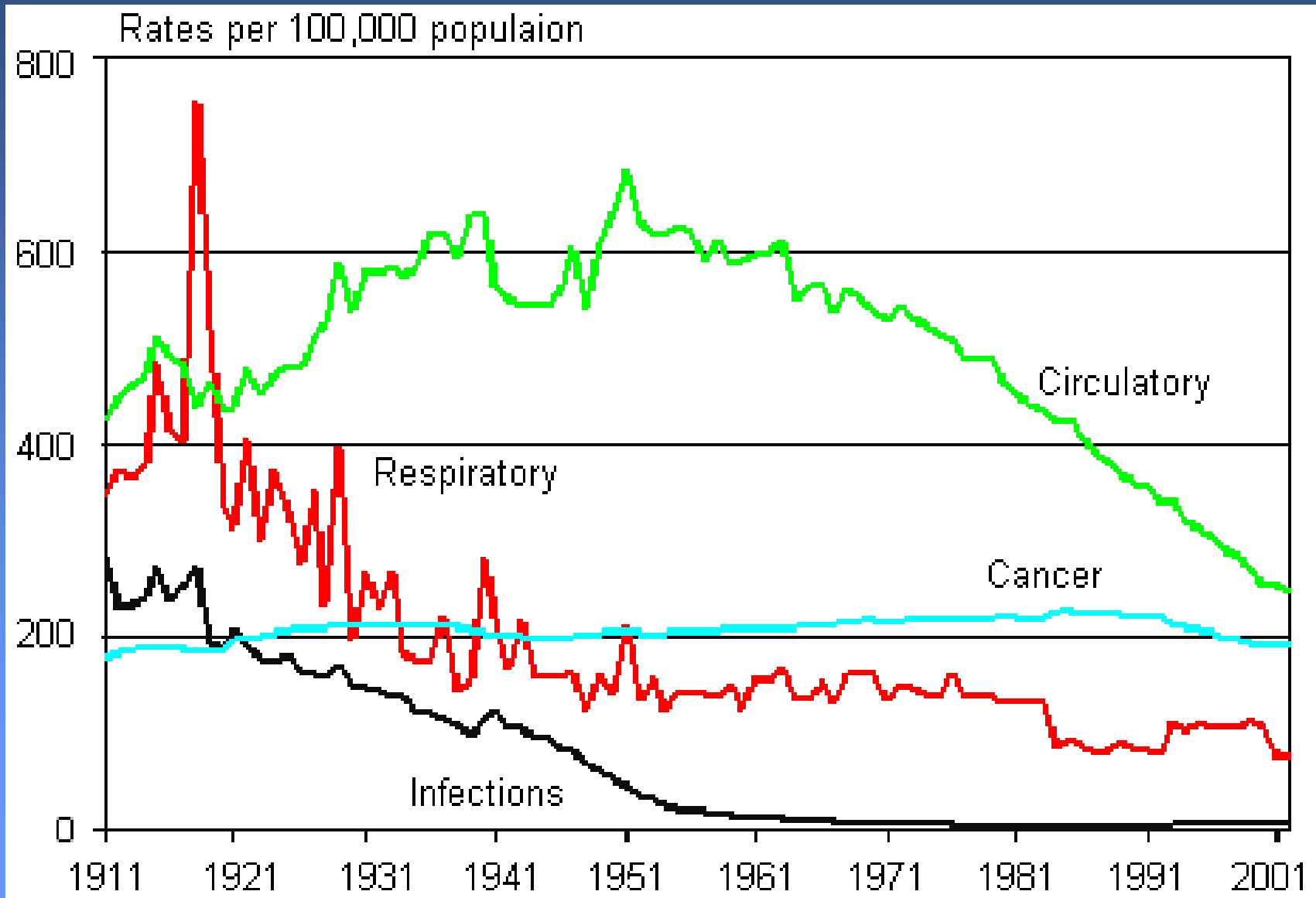
Professor Norman Ratcliffe

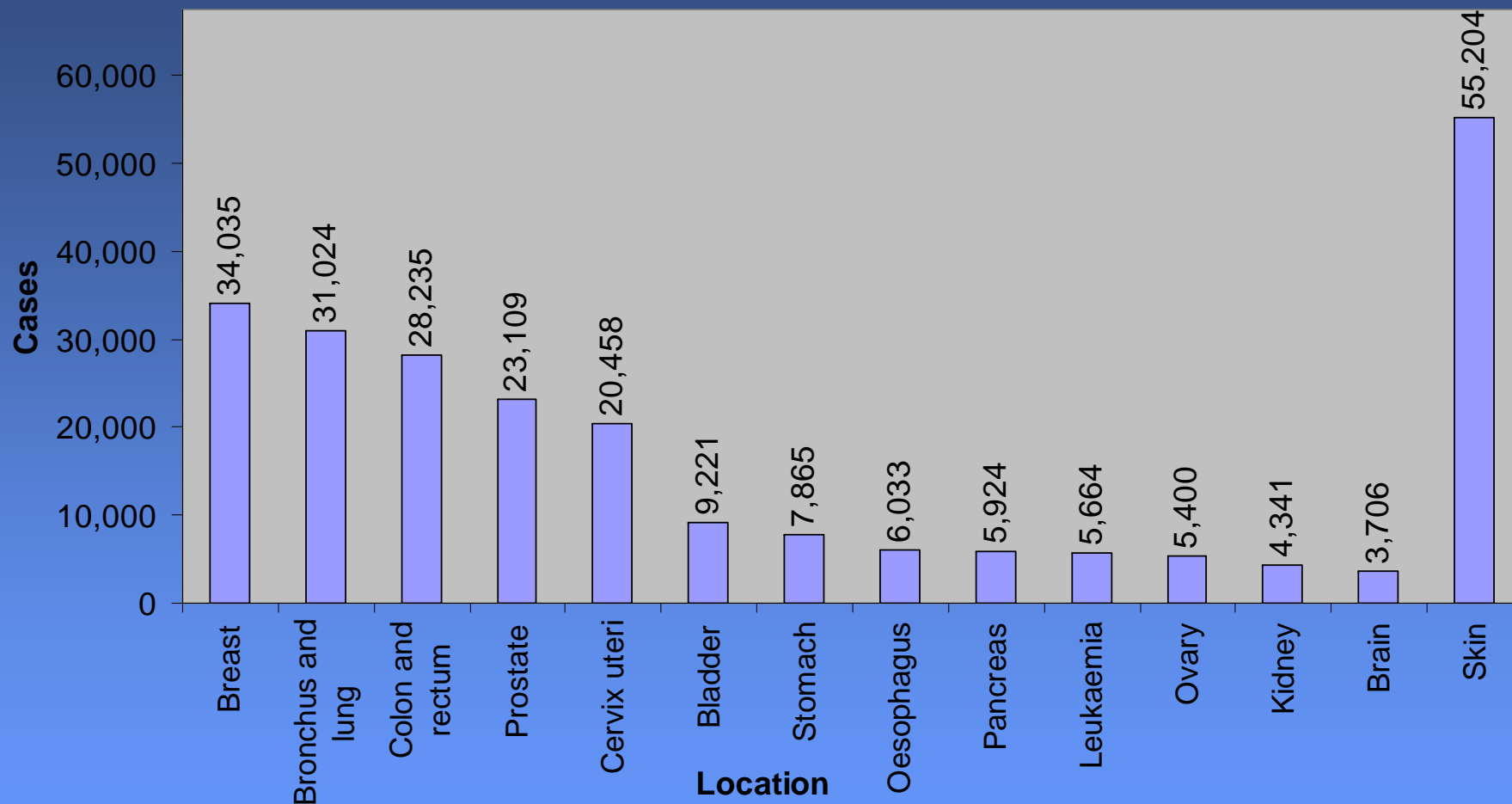
Deputy director Research Centre for Analytical,
Material and Sensor Sciences, UWE

VOCs from Humans



- Breath
- Saliva
- Sweat
- Urine
- Stool
- Semen/Vaginal discharge

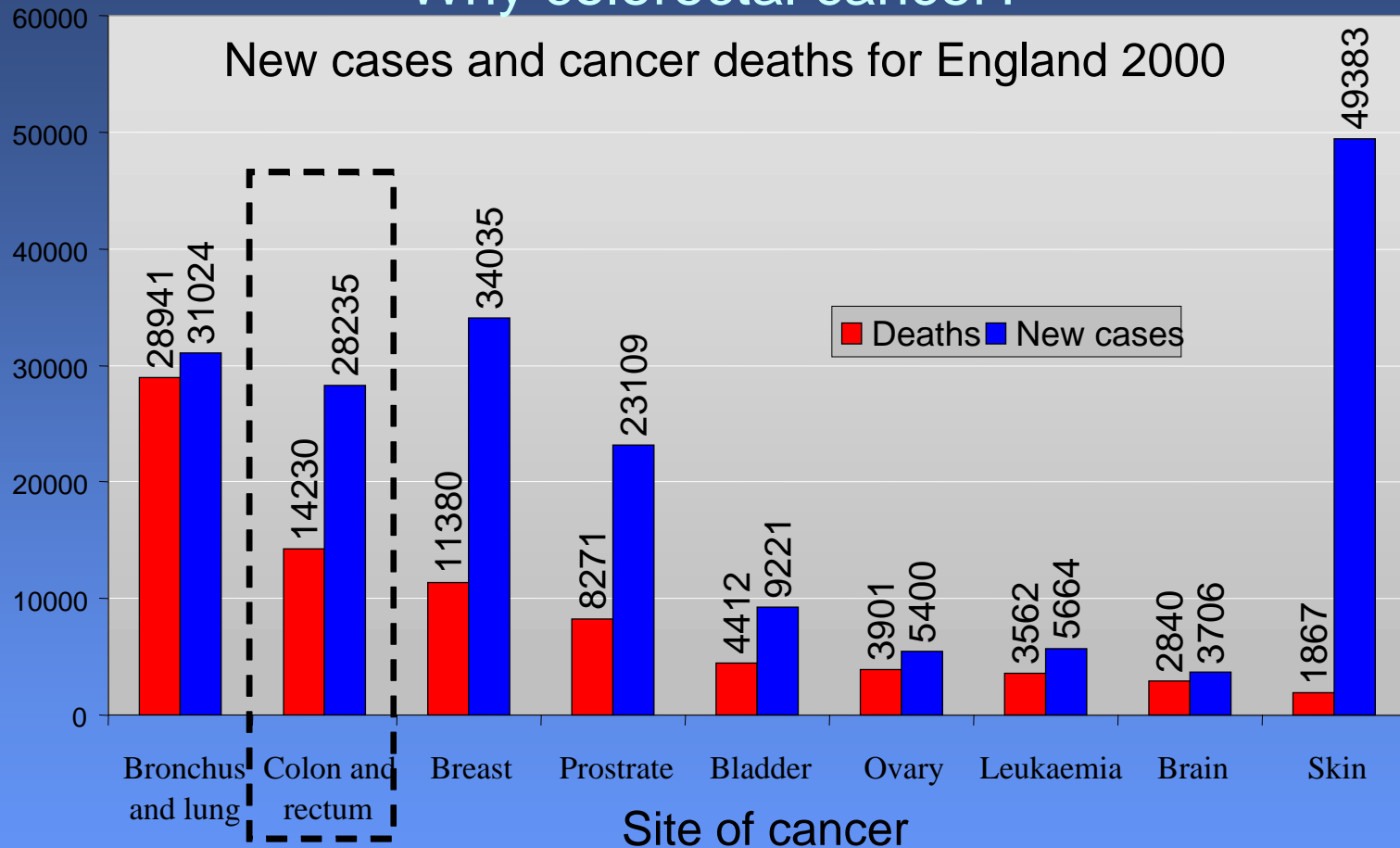




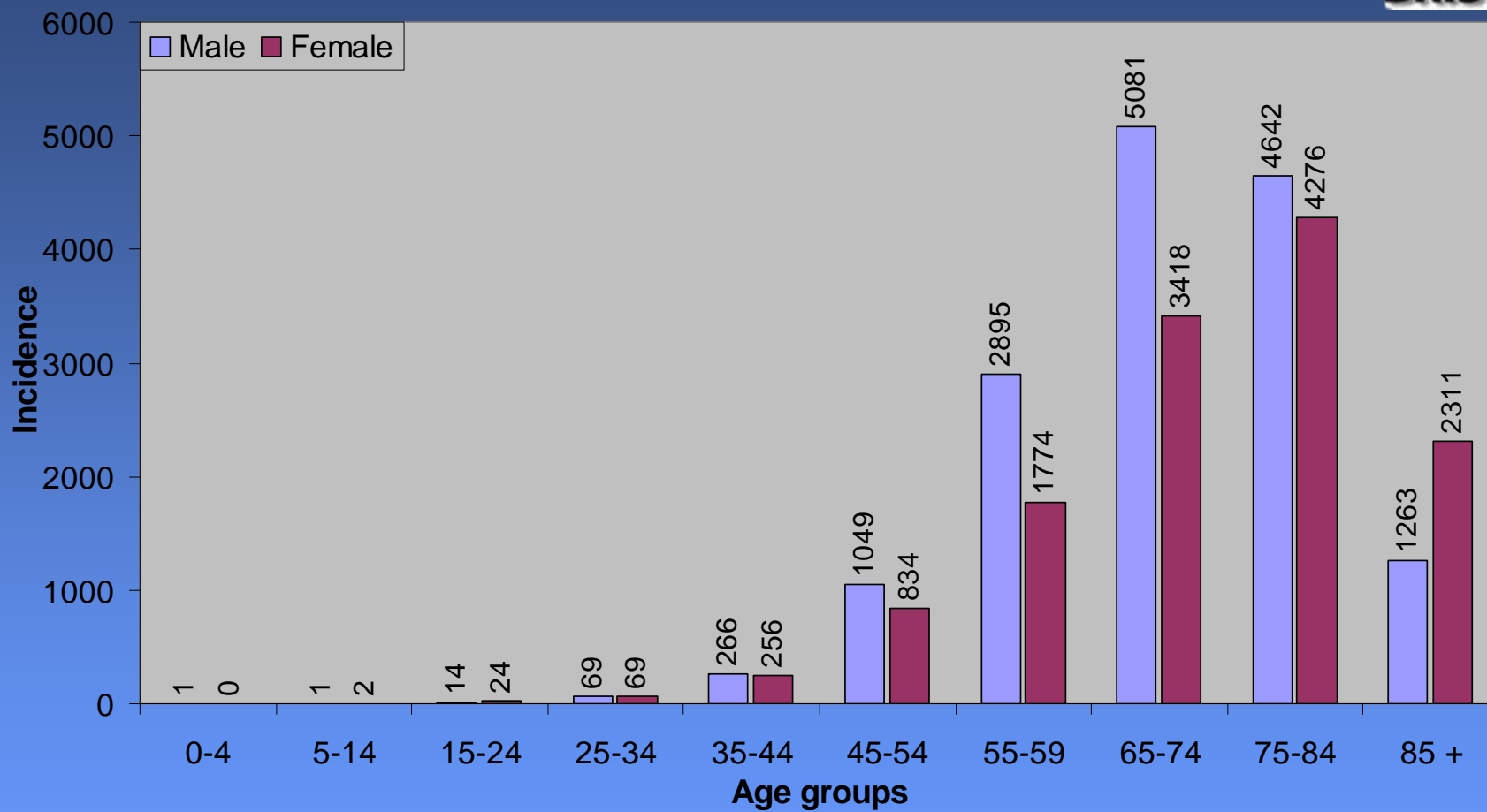
Incidence rate for common cancers by type for England and Wales for the year 2000⁴

Colorectal cancer study

Why colorectal cancer?



- Colorectal cancer accounts for 14% of all diagnosed cancers in men and 12% in women
- It is currently the second biggest killer of all cancers in England



FDA approved breath tests



NO detection- Asthma: causes 2 million emergency room visits, approximately 500,000 hospitalizations/annum

C-13 CO₂ -*H. pylori* detection

Pentane -marker of acute cardiac allograft rejection.

Unknown-blood glucose meter with a standard-issue cellphone

Hydrogen-bacterial overgrowth, malabsorption

VOCs from urine for disease diagnoses



Urinary Tract

Infection

>[NH₃]

>[CH₃CO₂H]

Av. 100ppm

Healthy

Av. 3ppm

Bacterial

vaginosis

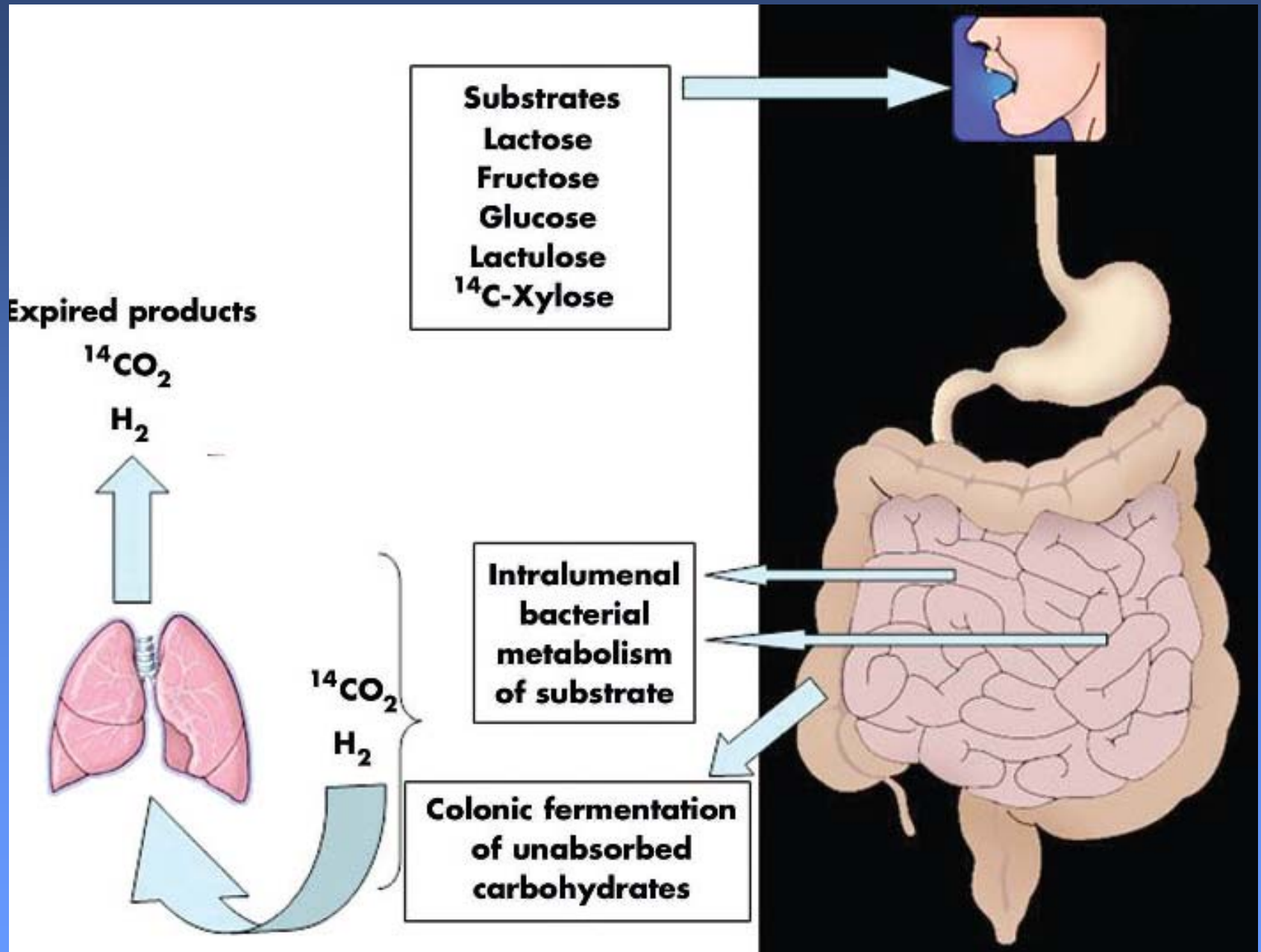
>[NH₃]

>[CH₃CO₂H]

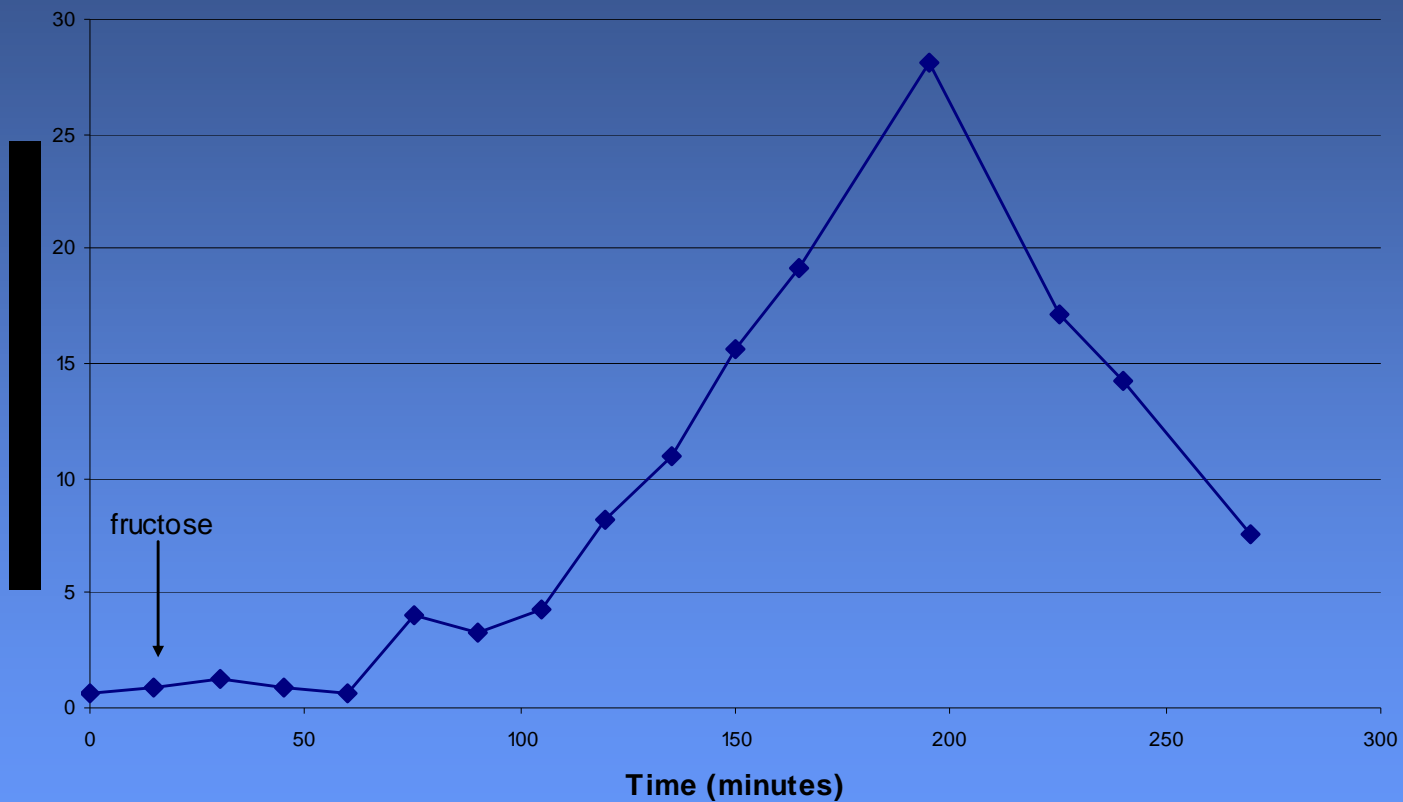
>900ppm

Healthy

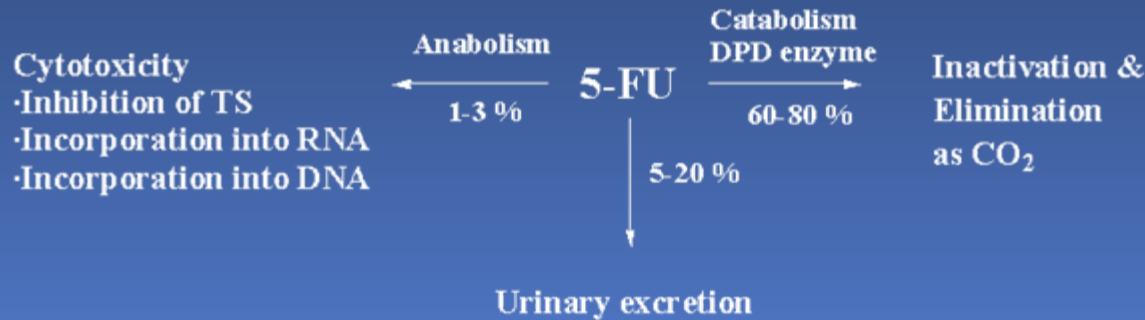
<900ppm



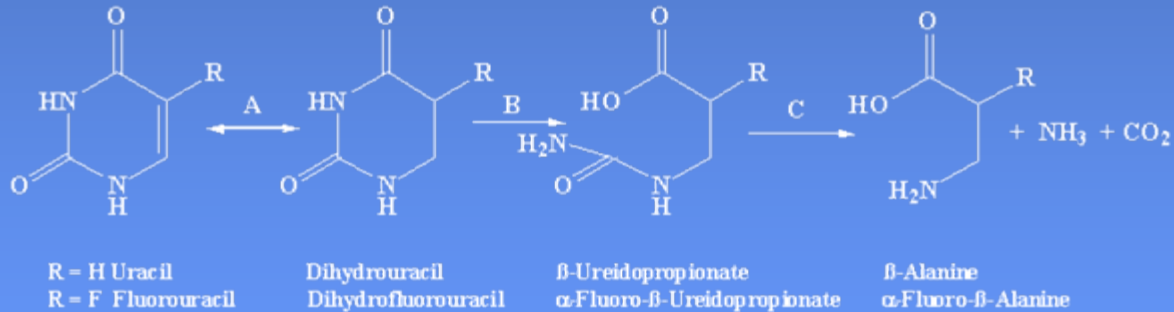
Change in hydrogen concentration on breath (ppm) after ingestion of 25g of Fructose in solution



5-Fluorouracil metabolism



Pathway of pyrimidine base catabolism in mammalian systems



- A Dihydropyrimidine dehydrogenase DPD
- B Dihydropyrimidinase DPHD
- C β-Ureidopropionase

Frequency of DPD deficiency

5-Fluorouracil metabolism Partial deficiency

Caucasians 3-5%

African Americans 8-12%

Complete deficiency 0.5-1%

Personalize 5-FU mediation



DPD enzyme activity

Normal activity
no reduction in dose
necessary, 12 mg/ kg

Partial deficiency
dose needs to be
lowered to avoid
toxicity
4-10 mg/kg

Profound deficiency
Alternate therapy
recommended

Tuberculosis Diagnostics



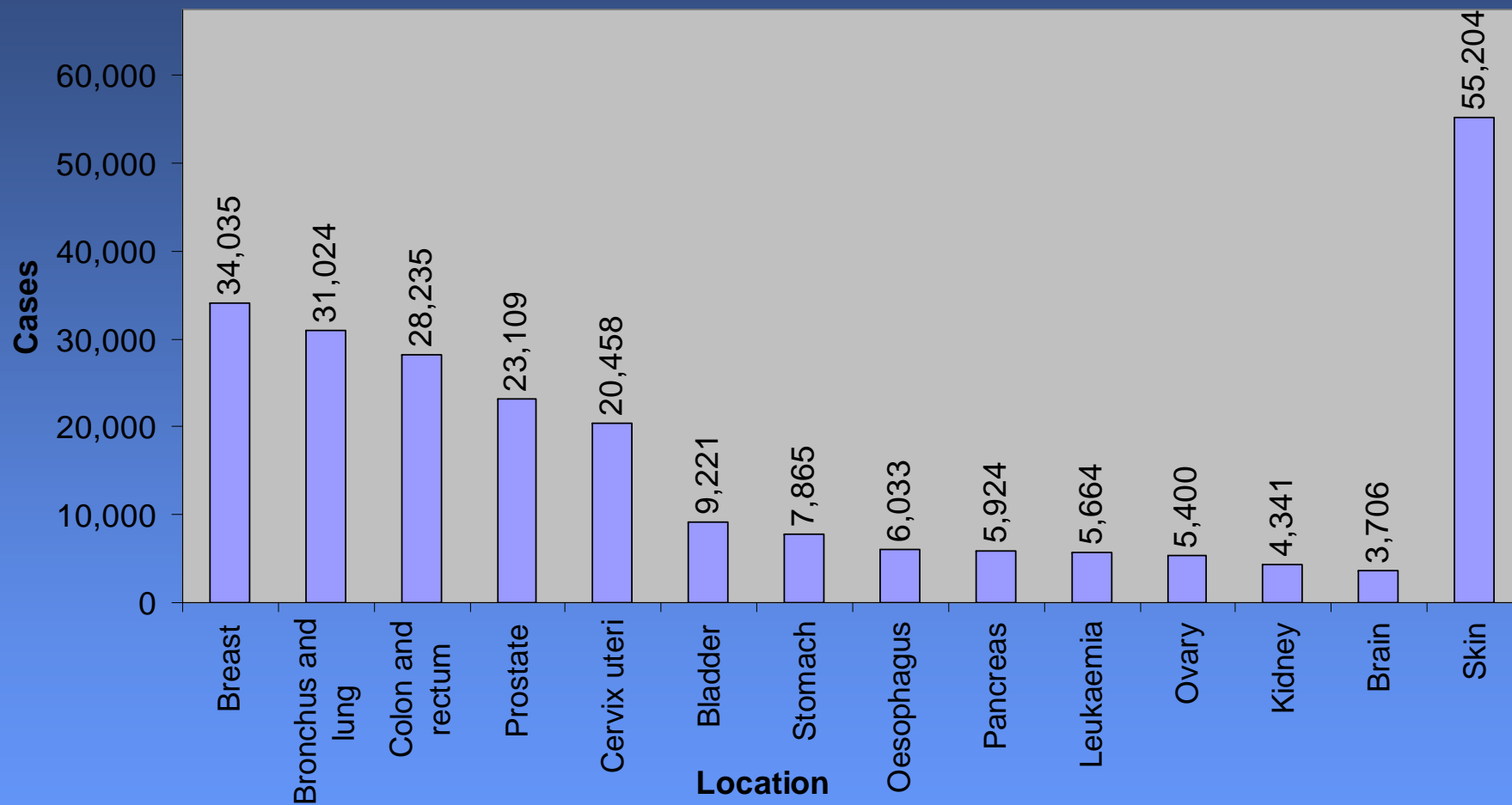
- Approximately two million people worldwide die of TB each year.
- In 1997, there were 385 deaths in England and Wales from TB, according to the Public Health Laboratory Service.



The situation for TB testing

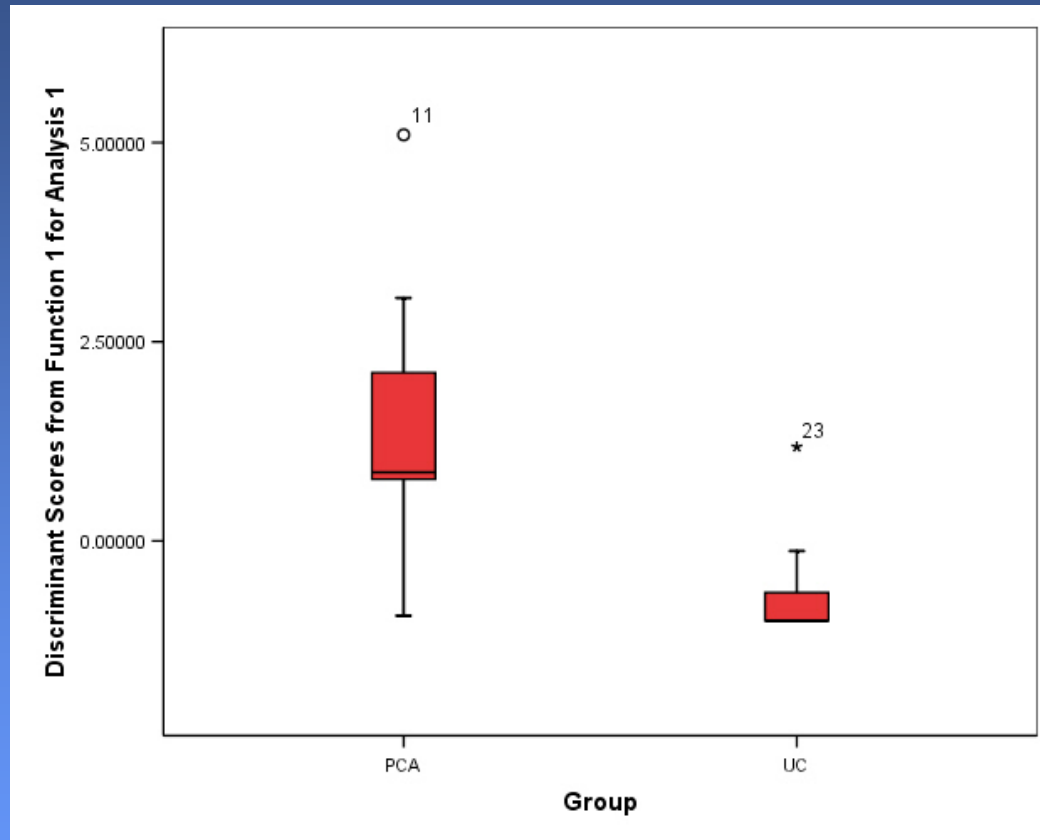


- **WHO-large, untapped global market exists for improved TB tests**
- HIV is fuelling TB epidemics in many countries and multi-drug resistance is a growing threat. 1.7 million people a year die from TB, many because the infection goes undiagnosed, or is diagnosed too late to be cured.
- Point-of-care screening – (at clinics and health posts), a potential available market of some 79 million patient evaluations a year.
- VOC biomarkers-University of Stellenbosch and the Royal Tropical Institute in Amsterdam



Incidence rate for common cancers by type for England and Wales for the year 2000⁴

Novel biomarkers for prostate cancer: a pilot study



Worldwide the use of PSA as a screening test remains controversial due to its low specificity (38%) and the rate of false negatives (up to 20% with PSA level <4ng/mL prostate cancer being the most common male malignancy in the Western World, there is no definitive diagnostic test. More than 30,000 cases are detected in the UK each year (2006), usually by a combination of digital rectal examination, serum prostate specific antigen (PSA) and trans-rectal ultrasound-guided prostate biopsy.

Diarrhoea



- Diarrhoea afflicts 2.7 billion people annually, worldwide
- 6,800 children still die as a result, each day
- Diarrhoea-specific mortality in children < 5y in Africa is 1.1%
- Rotavirus causes 56,000 hospitalizations pa in USA
- In England and Wales, 50,000 cases of *Clostridium difficile* occur pa, costing the NHS > £60M
- 1% of Europeans contract *Campylobacter* each year
- Despite technical advances, there is a diagnostic delay of several days between sample collection and lab. diagnosis
- Eg: Diagnosing *Clostridium difficile* in the UK takes 8.2 days (average)

On-going work on VOCs from diarrhoea



- **Infectious diseases:**
 - Cholera (Bangladesh, Uganda)
 - *Clostridium difficile*
 - *Rotavirus*
- **non-infectious diseases:**
 - Ulcerative colitis
 - Crohn's disease
 - Colonic cancer

C.Difficile – dying for a diagnosis

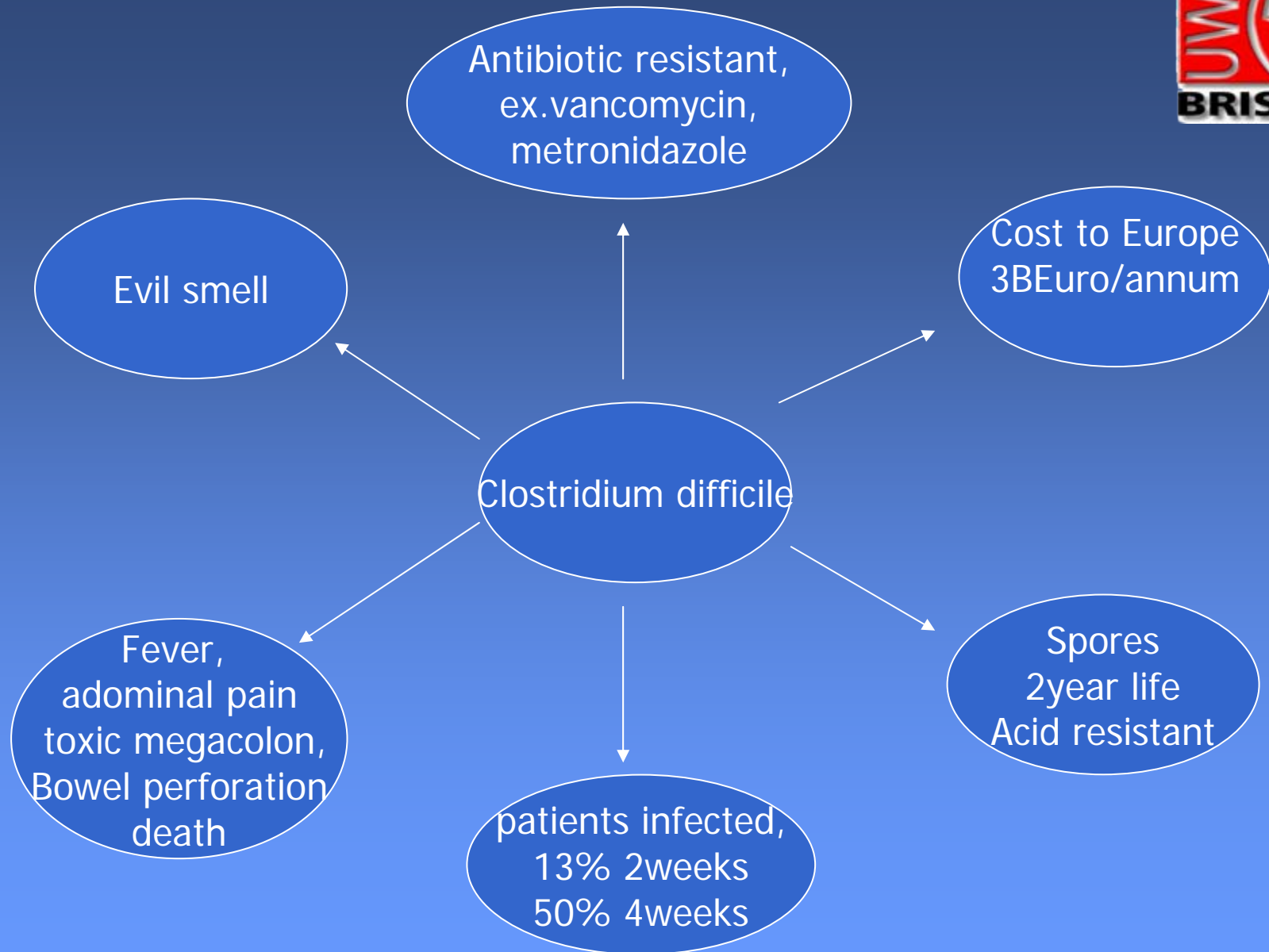


- **“Hospitals fail to halt spread of superbug that kills 4,000 a year”**

The Independent, 27 April, 2007

- **“Superbug claims 49 lives in top hospitals”**

The Observer, 1 October, 2006

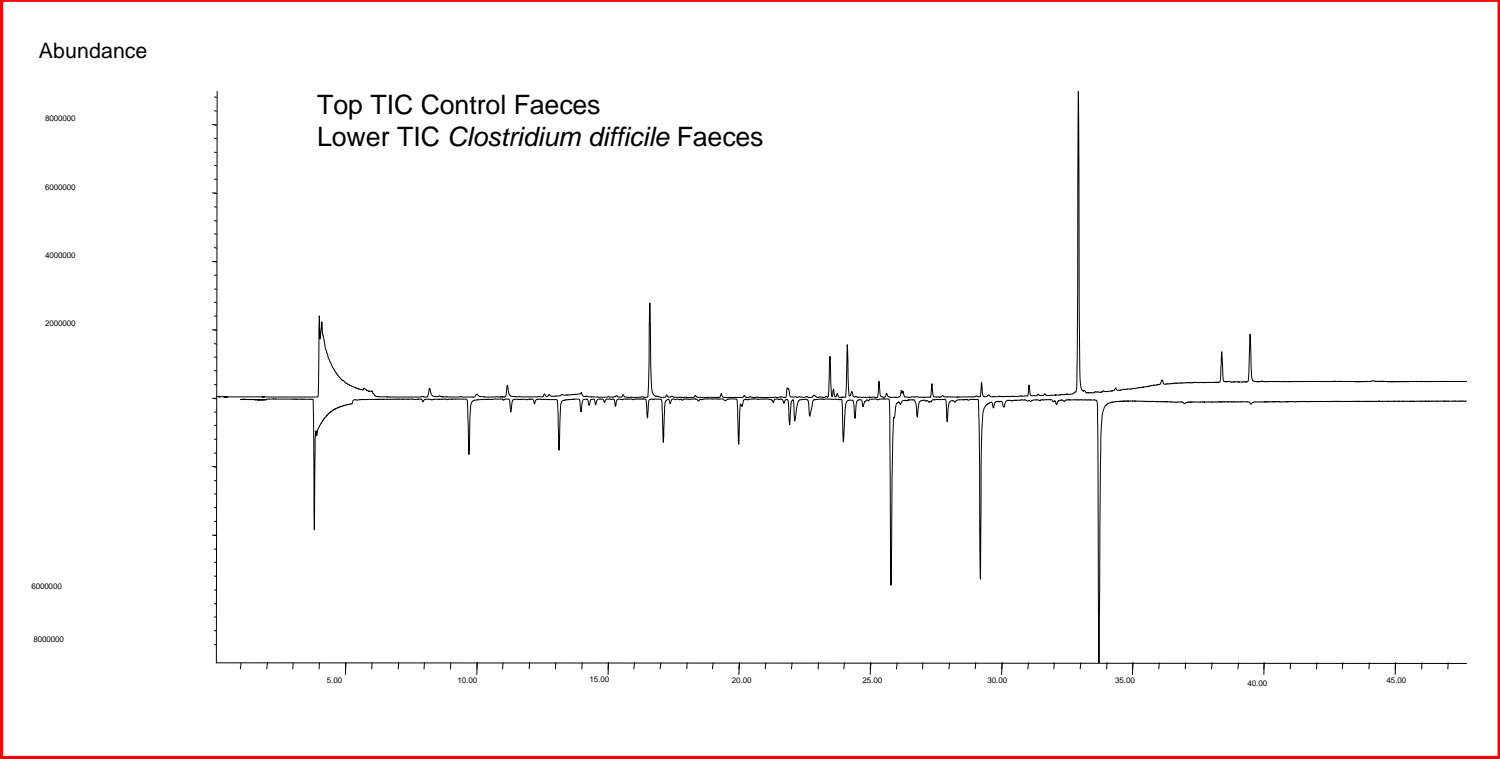
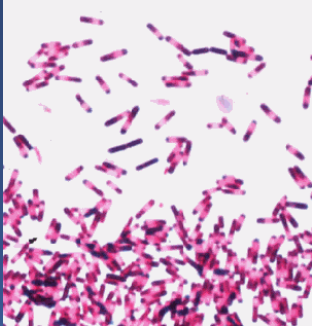


Norovirus - dying of ignorance

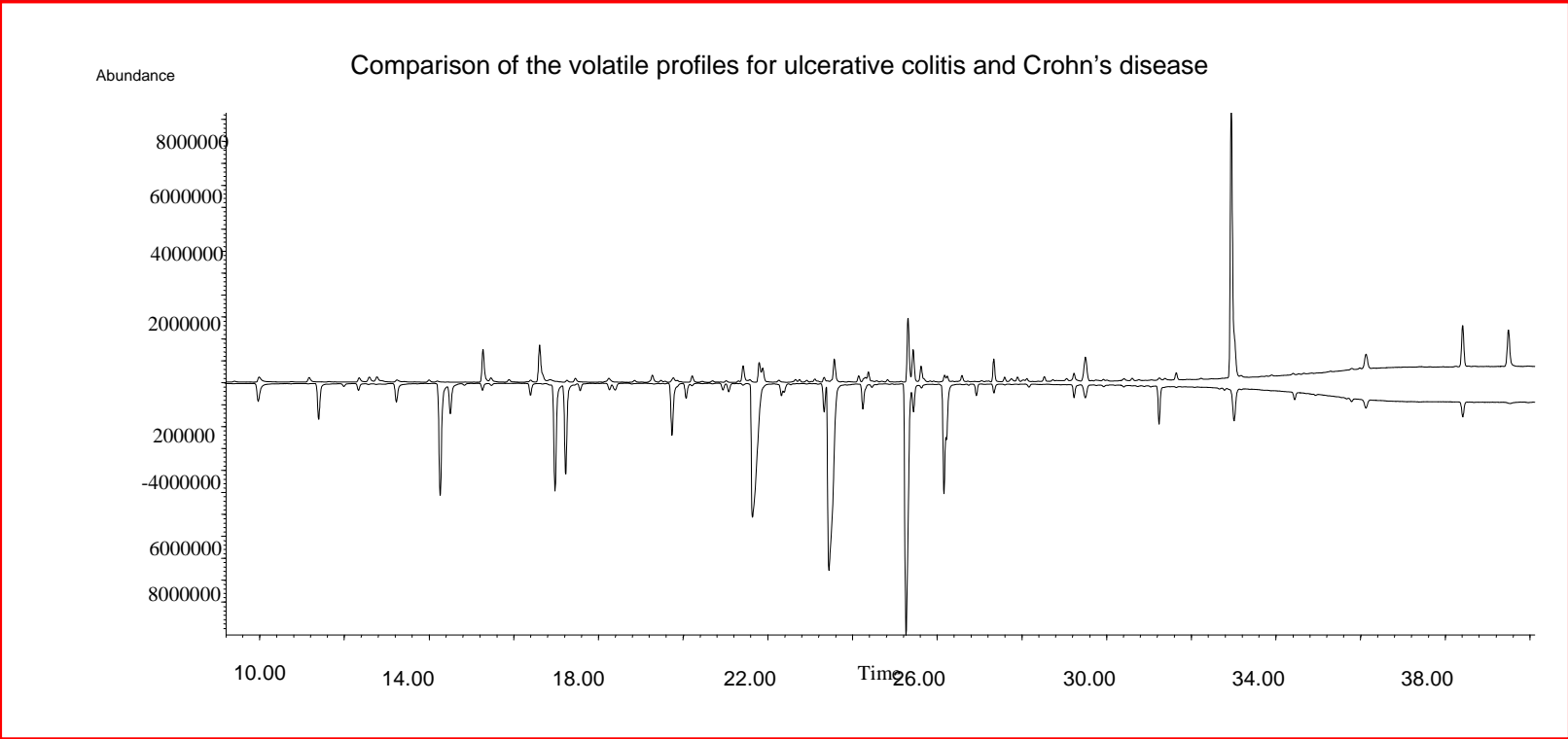
- “Delays in receiving Norovirus results from the Virology Department had an impact on the outbreak management. At times results were not available for up to 10 days after being sent. Inevitably there is a significant demand on the virology laboratory, which serves all acute hospitals and the community in the area.”

North Bristol NHS Trust 2006

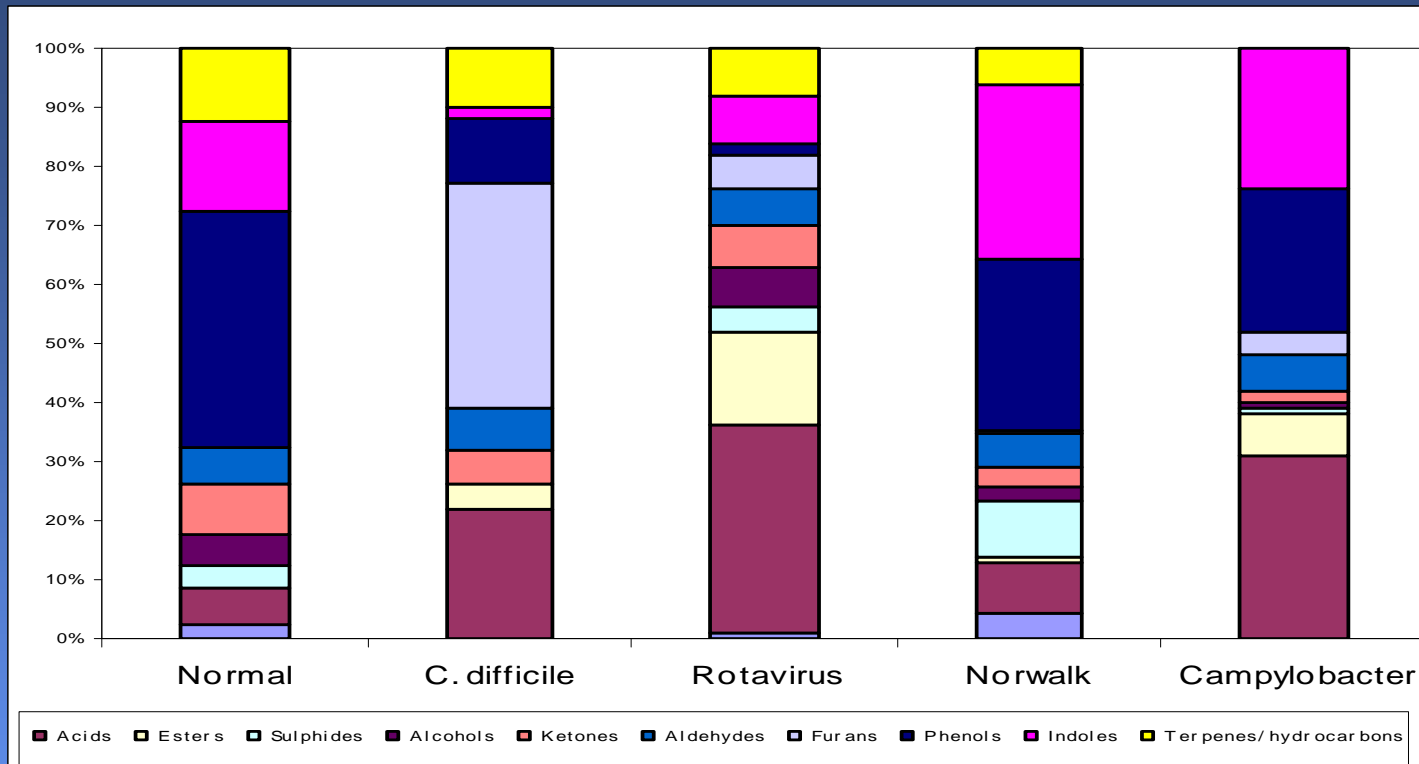
TIC of control and *C. difficile* samples



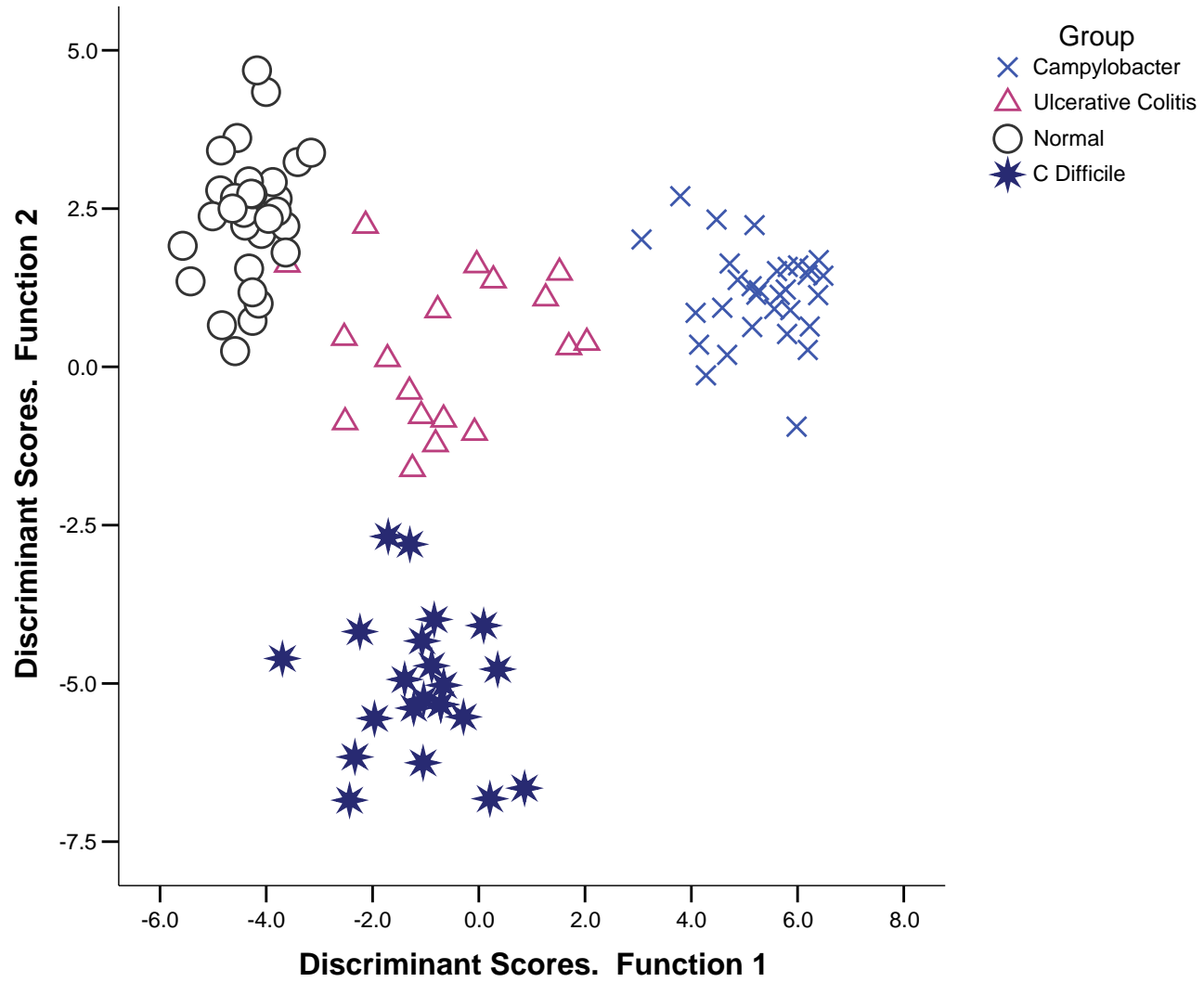
TIC from patients with IBD: ulcerative colitis vs Crohn's disease



Comparison of VOC classes from patients in the preliminary study diagnosed with infective diarrhoeas and controls



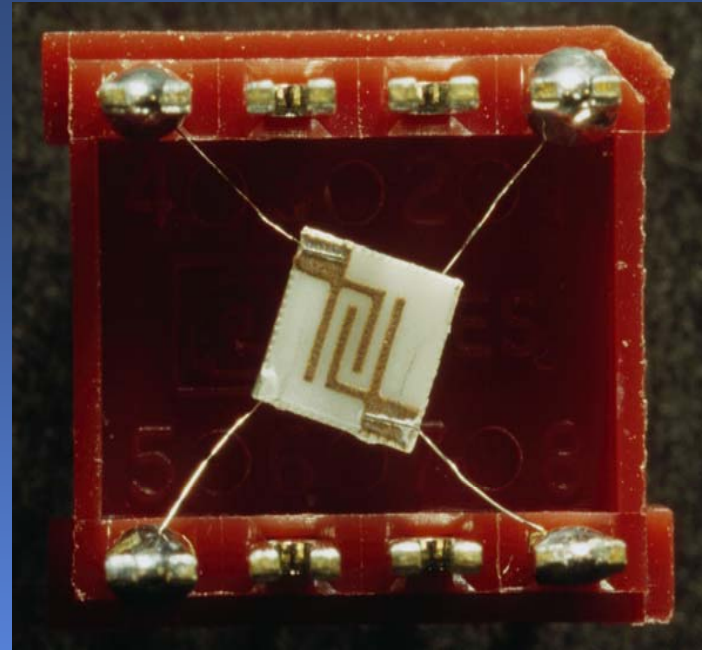
The profile of the volatile organic compounds extracted from the samples gave characteristic patterns for the specific gastrointestinal condition present. There were also some unique chemical markers present in the odour analysis.



Ceramic sensors for VOCs

Construction

Interdigitated electrodes
 vacuum evaporation of SnO_2 in
 oxygen plasma (doped with
 precious metals)
 thick metal oxide composites
 heated to $350 - 450^\circ\text{C}$

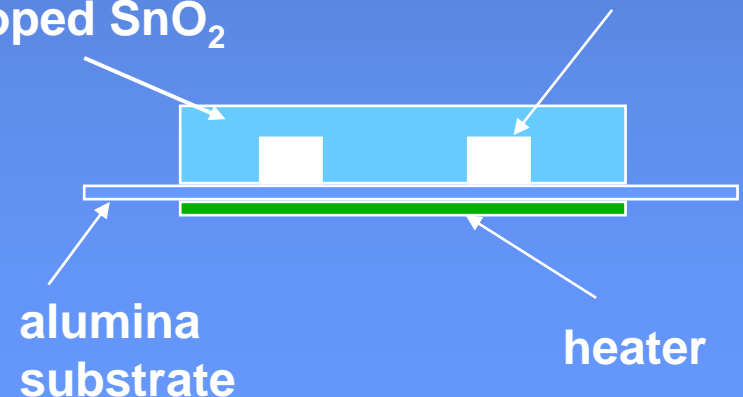


Mode of action

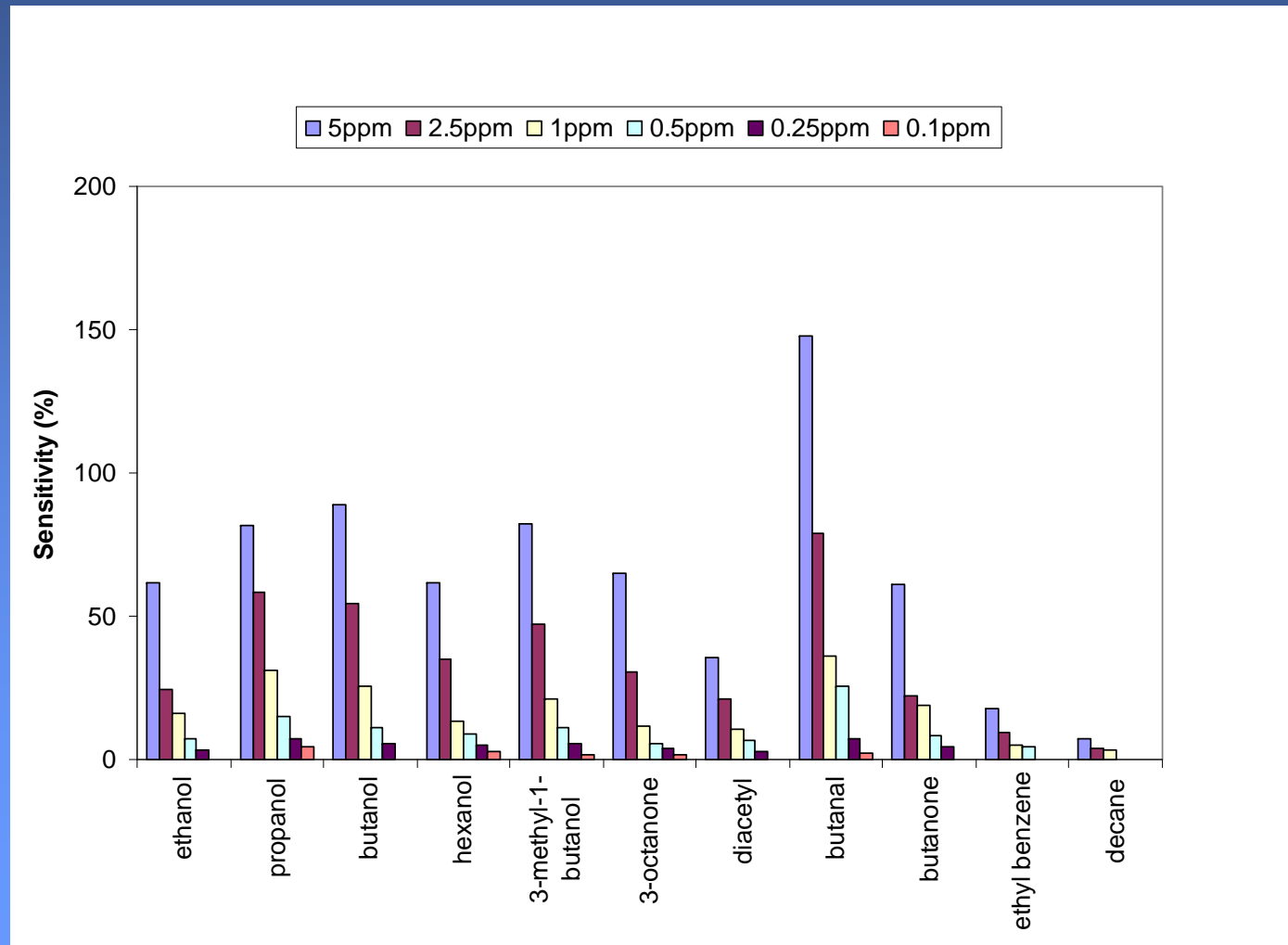
SnO_n absorbs O_2
 metal catalyses oxidation of VOC
 resistance changes to 95%
 maximum in 30 s return to
 baseline < 5 min air purge

interdigitated electrodes

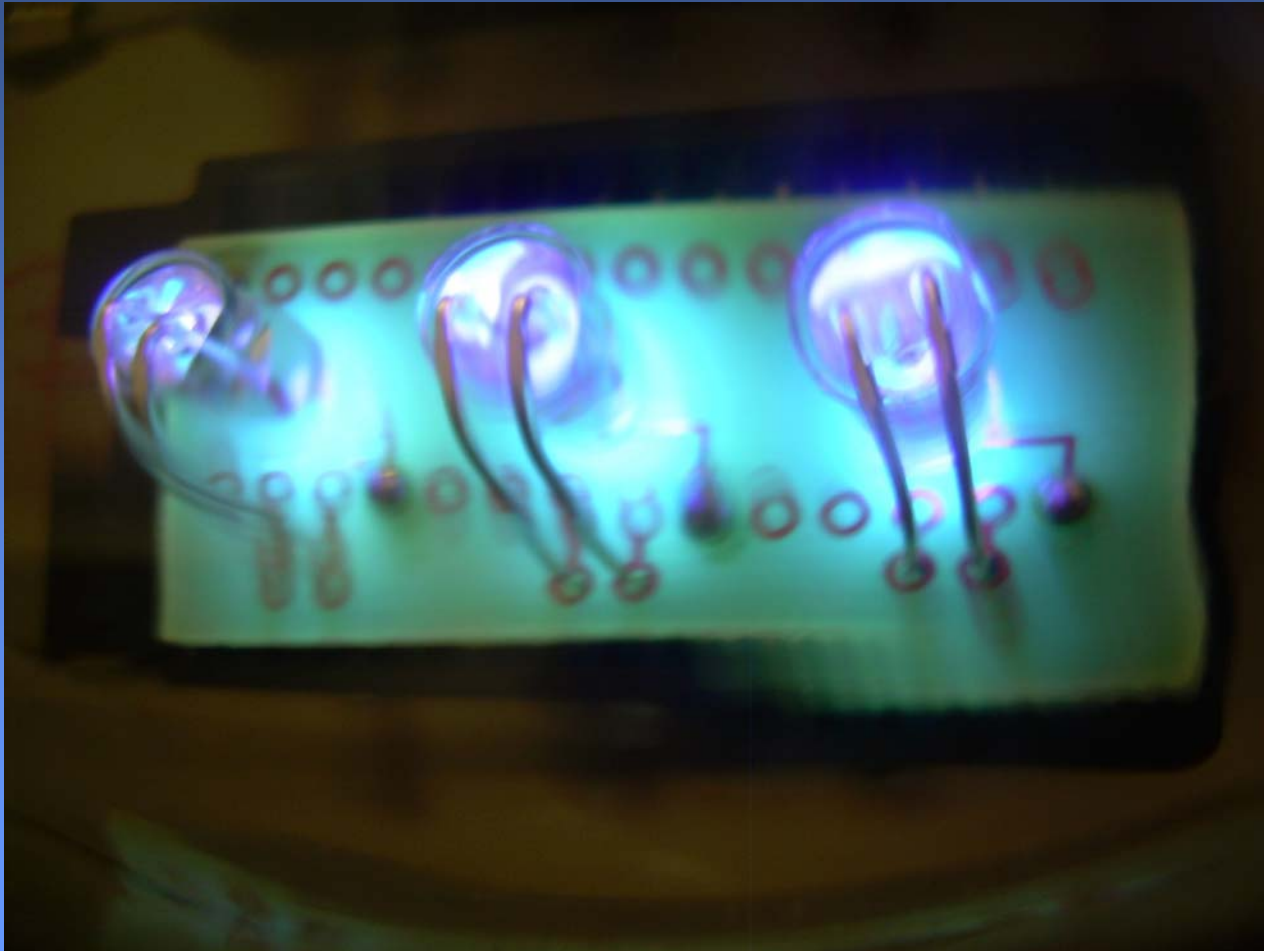
doped SnO_2



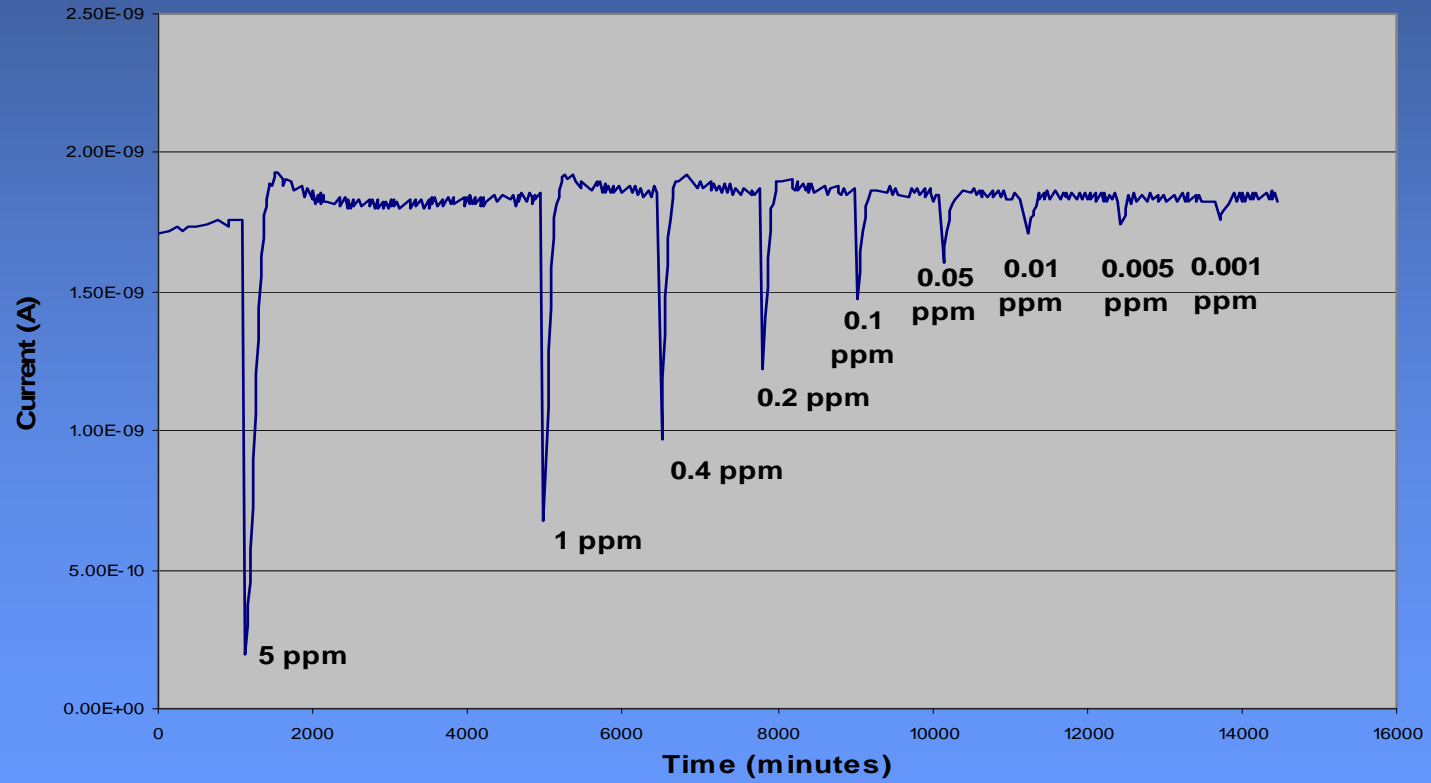
The response profile of the tin dioxide/indium oxide composite sensor when exposed to 11 vapours at six different concentrations under a constant flow of humidified air (100% R. H.) at 1 litre/min



UV activated nano-particulate ceramic chemiresistors



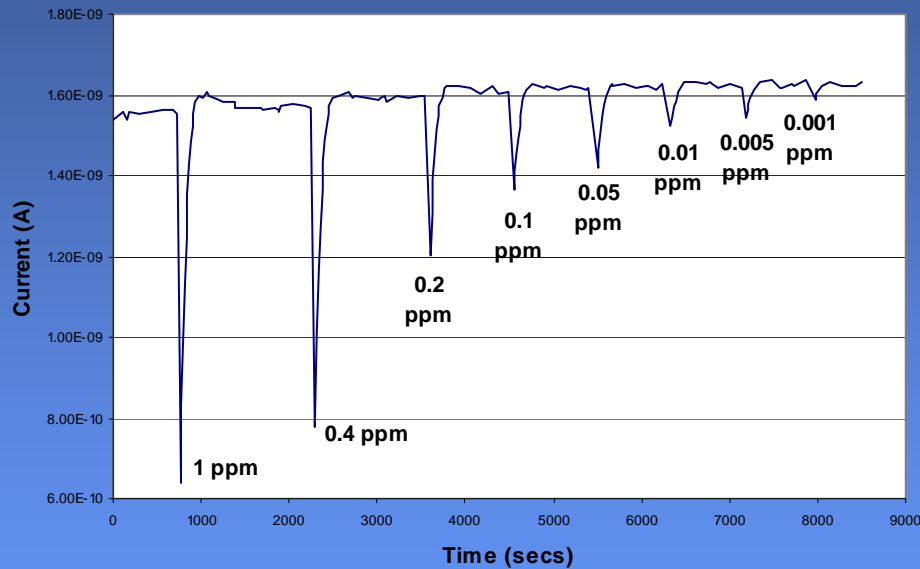
Acetone detection



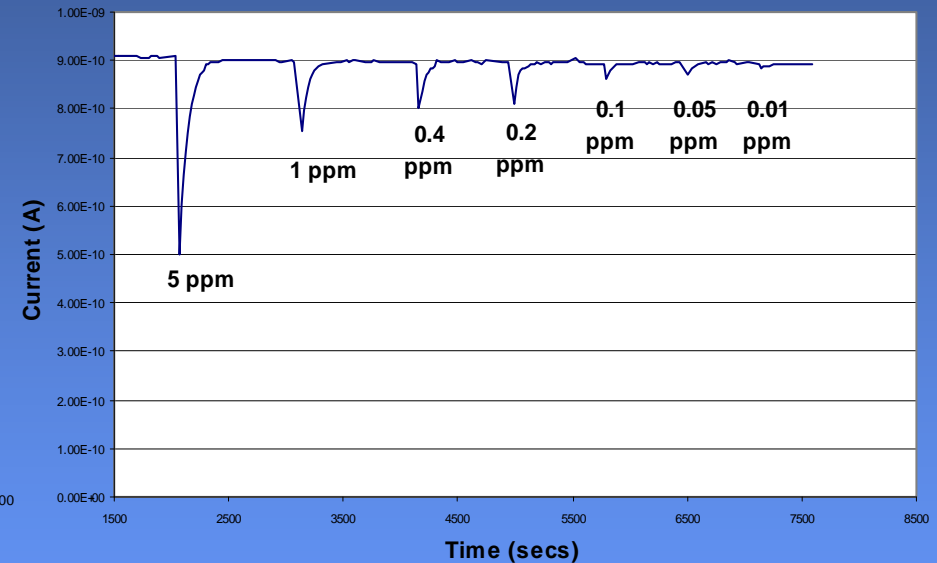
Acetaldehyde and pentane detection



Acetaldehyde Responses on nanoparticulate ZnO



Pentane Responses on nanoparticulate ZnO



Summary

- Worldwide increase in research in the area of volatile analyses for disease diagnoses
- Commercial tests have been proven in the marketplace
- The analyses are non-invasive and appealing to patients
- Many potential applications e. g. diagnoses of TB, diabetes, lung cancer, prostate, bladder cancer
- VOC profiling distinguishes diseases in GI diseases and prototype sensors have been built that distinguish between diseases

Acknowledgements



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- Volunteers