Evidence-based toxicology: does it work for long-term toxicity testing?

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What is evidence-based toxicology?

- **Toxicological considerations and regulations have certainly contributed to making our lives safer and longer.**
- **However, there is considerable reservations that current protocols for drugs and exposure to chemicals may be inefficient and sometimes inappropriate or missing toxicity in susceptible individuals.**
- **On the other hand, there is still a need to understand the risk from potentially toxic agents as in REACH legislation, nanotechnology and biotechnology products.**
- **But is this getting us further and further away from reality as far as human health is concerned.**
- **<u>Evidence-based toxicology envisages using all scientific information from molecular and clinical to epidemiology to make the best scientific decision about risk.</u>**

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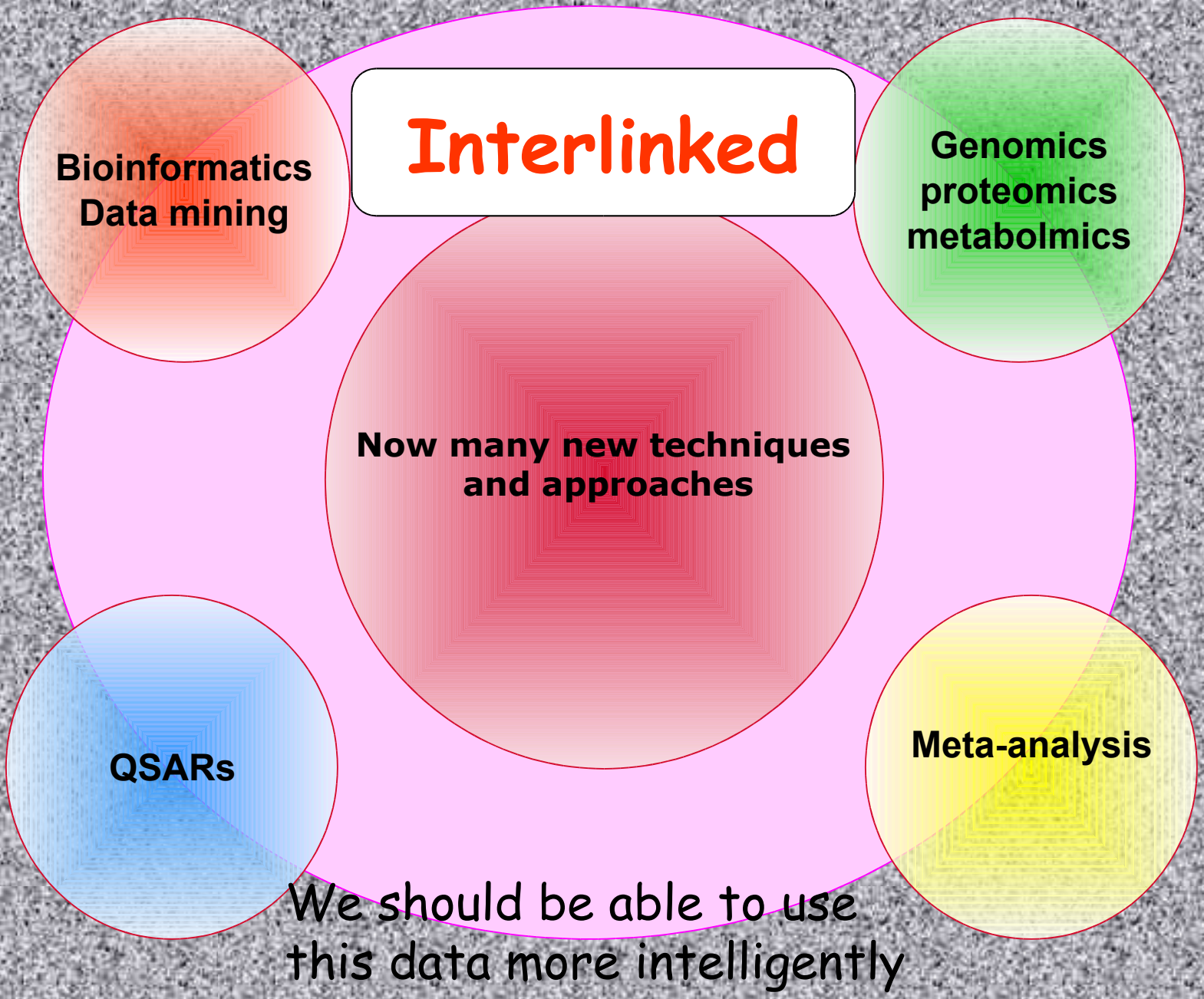
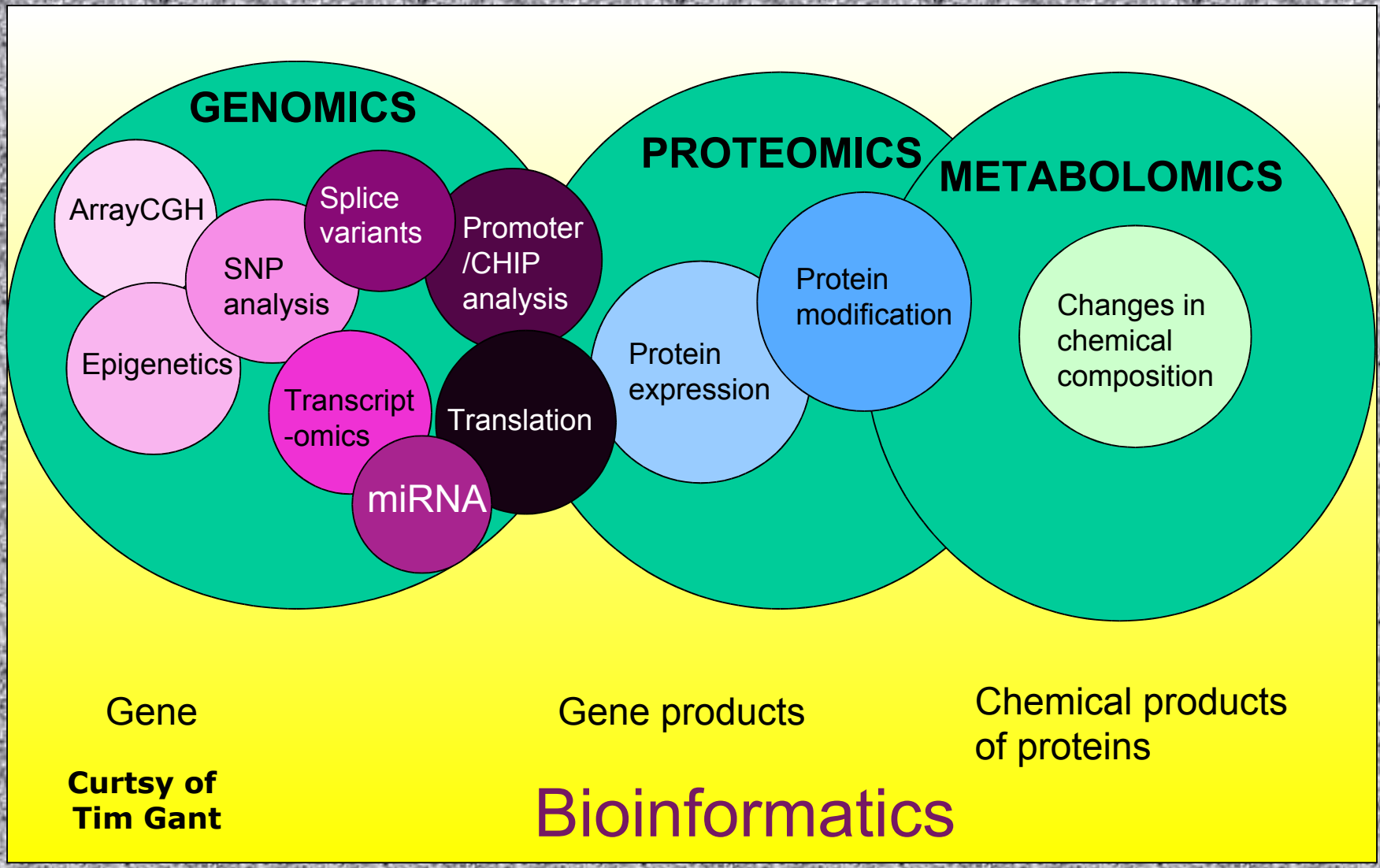
- **In many ways this is a sensible approach**
- **Perhaps with more and more regulation there is too great a mind-set using established tests**
- **Both in Europe and the US there are voices saying we should evolve toxicology --- be <u>proactive</u>**
- **Importantly, toxic mechanisms are no different from other pathogenic mechanisms**
- **Should be much greater use of all clinical, molecular and environmental information to make decisions**
- **Not always easy to see how in practice**

- **In the UK, the Committee of Toxicity TDI assessment for dioxin considered all aspects of molecular, human and *in vitro* and *in vivo* experimental data by multidisciplinary members, many not 'toxicologists'.**
- **Ultimately though, only poor *in vivo* data had to be used be used to produce a TDI demanded by government and public.**
- **Ironically, new statistically more powerful studies (*Bell et al Tox Sci* 2007) have failed to confirm the sperm no. endpoint but shown a delayed puberty effect.**
- **Still very difficult to know what this means for human health.**


Interlinked
Bioinformatics
Data mining
Genomics
proteomics
metabolmics
Now many new techniques
and approaches
QSARs
Meta-analysis
We should be able to use
this data more intelligently



Genomic signatures

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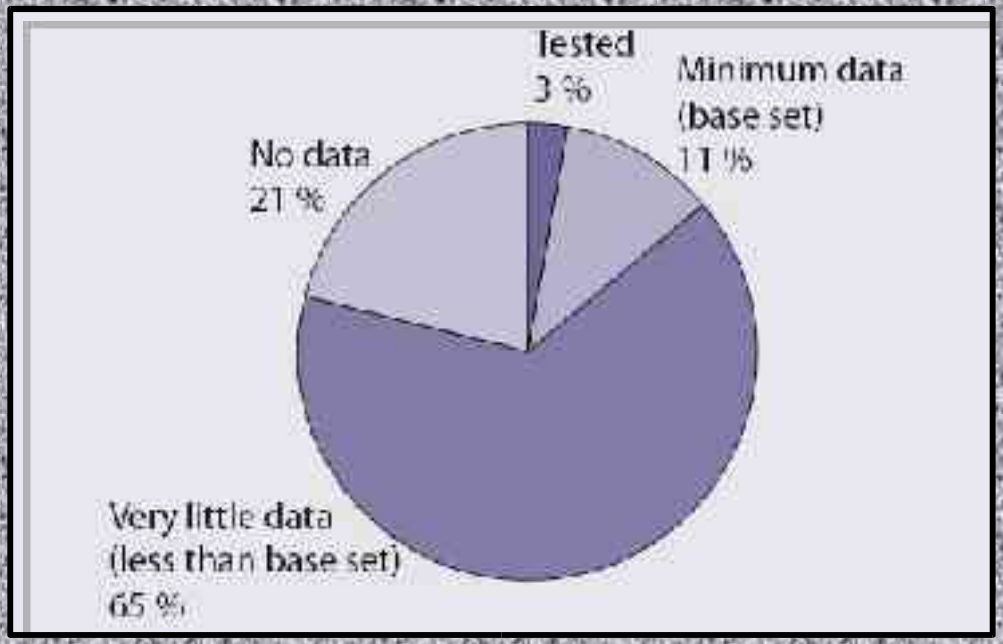
If used intelligently, genomics and informatics should help REACH evaluations



Curtsy of
Tim Gant

Could be difficult to handle all the information

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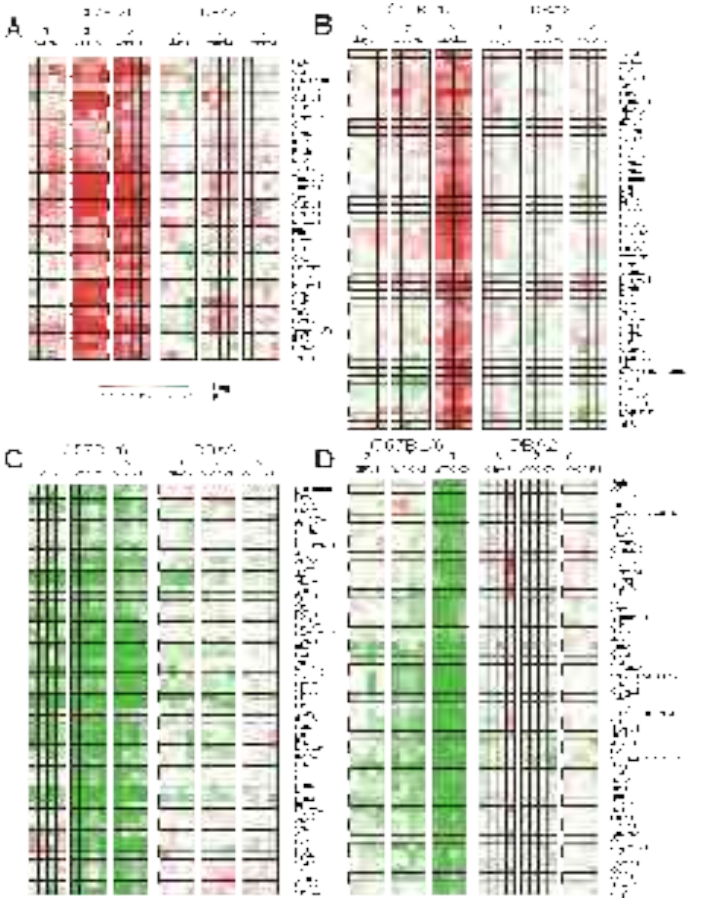
Very seductive but may only tell you what a pathologist says!

Ultimately, we need to understand the mechanisms or mode of actions and whether these are pertinent to humans

We need to have future toxicologists and regulators understand wider concepts

Chronic dioxin toxicity



Davies et al *Chem Res Toxicol*

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Recommendations from Stakeholders

MRC ABPI Academy of Medical Sciences, BioIndustry Association, Dept of Health, Food Standards Agency, Health Protection Agency, Pesticides Safety Directorate

Integration

More synergy/integration of different disciplines of toxicology research, incl.

- Fundamental mechanisms
- Specific chemicals/drugs
- Animal physiology
- Clinical studies
- Epidemiology
- Risk assessment

Training

Address shortage of well-trained toxicologists

- Incentives for good students to pursue career in toxicology
- Provision of high quality, multidisciplinary training environment

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MRC National Programme for Training and Capacity in Integrative Toxicology

- £2.25M MRC funding to pump prime National Programme
- Aim
  - Integrate research into fundamental mechanisms of toxicity with drug safety, environmental & regulatory toxicology
  - Train new generation of integrative toxicologists through 4 year rolling PhD Programme & CDFs
- Programme led by MRC Toxicology Unit
- Opinion Workshop held 5th Nov 2007, London

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ESTR Loci in Germline Mutation Induction by Chemical Mutagens

Germline mutation is difficult to study. Yuri Dubrova and Alec Jeffreys applied DNA repeat sequence loci mutation rate to humans exposed to radiation after Chernobyl and in Khazakhstan.

Nature, **380,** 673-686, 1996;
Mutat Res, **381,** 267-278, 1997

Similar technique developed in mice and compared to traditional methods

2+ months after exposure

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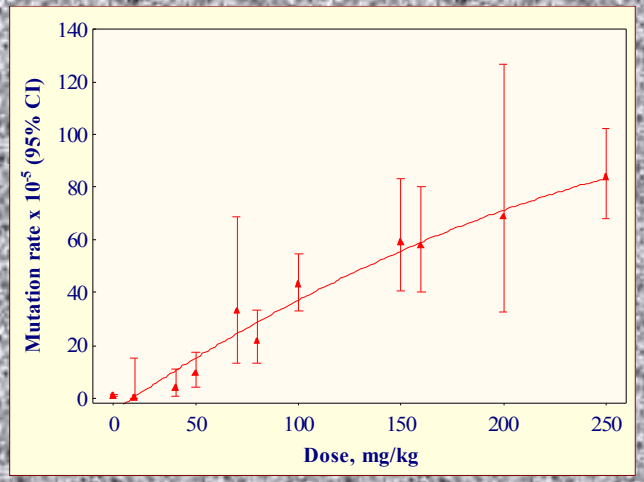
Spontaneous and radiation-induced mutations at mouse genes and ESTR loci

	Russell 7-Locus*	Dominant Visibles†	ESTR‡
Spontaneous mutation rate	7.95×10^{-6}	8.11×10^{-6}	5.56×10^{-2}
Animals tested	1,051,869	225,017	252
Exposure, Gy	3 - 6.7	6 - 12	0.5, 1
Doubling dose, Gy	0.34	0.17	0.33

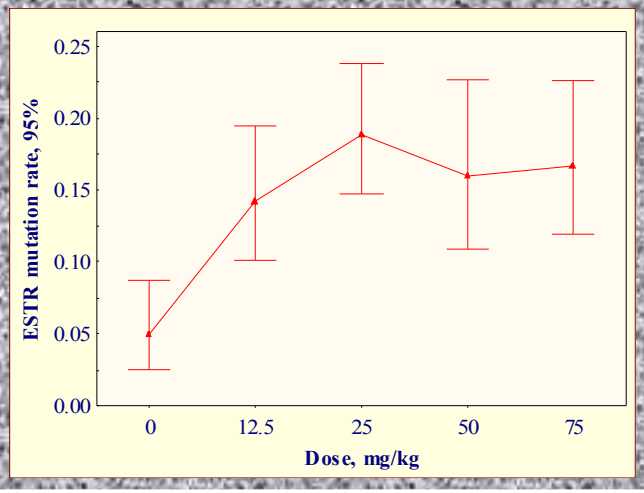
*Russell *et al.*, 1982, *PNAS*, **79**, 542-544
†Luning *et al.*, 1971, *Mutat. Res.*, **12**, 291-304
‡Dubrova *et al.*, 1998, *PNAS*, **95**, 6251-6255

Pre-meiotic (spermatogonia) germline mutation



7 locus test. 0-250 mg/kg ENU

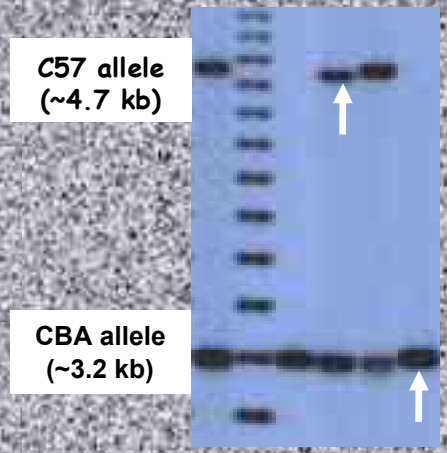
591,163 offspring (Russell *et al.*, 1979)



ESTR pedigree analysis. 0-75 mg/kg ENU

669 offspring (Vilariño-Güell *et al.*, 2003)

Single molecule PCR of sperm samples to assess mutations at the Ms6-hm ESTR locus in the germline of C57/CBA hybrid male mice 8 weeks after ENU 0-50 mg/kg



13 mice for study.

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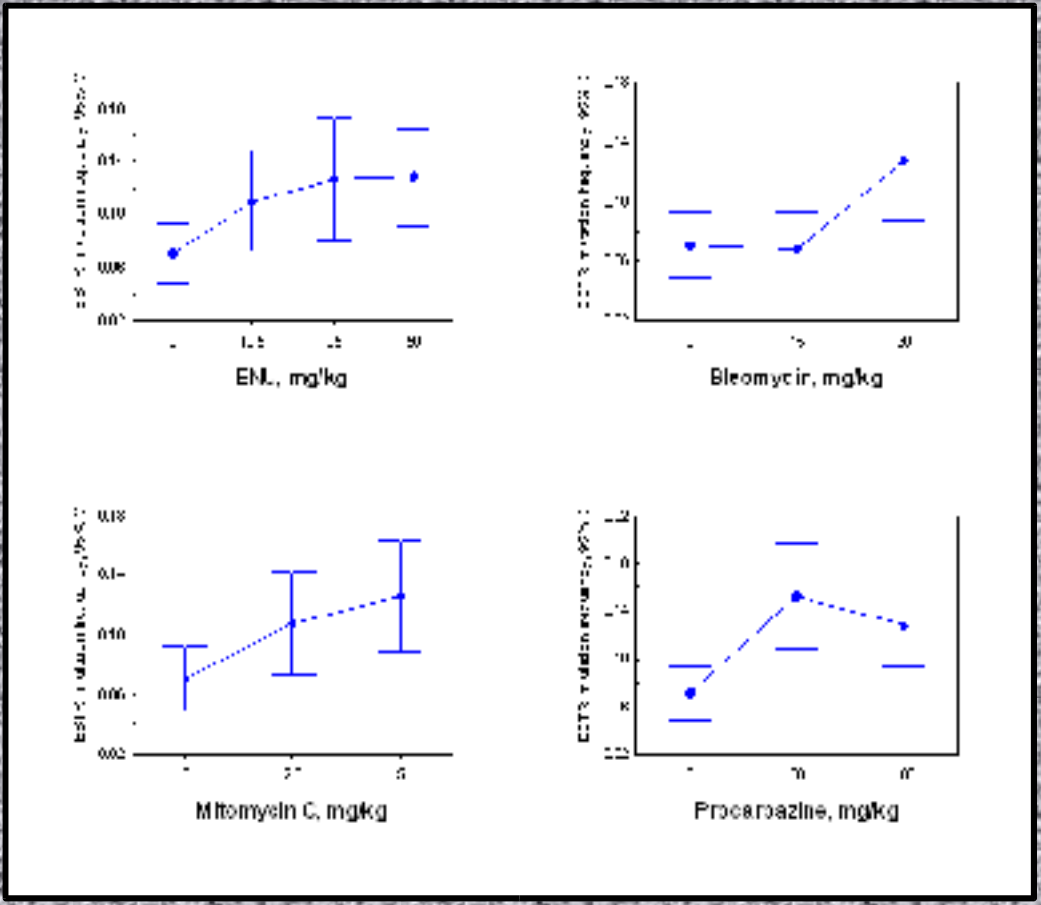
This technique used to compare anticancer drugs



- Detects ESTR mutation rates directly in <u>sperm</u> DNA of test/control mice.
- Obviates the need for mating mice as each sperm is a potential individual.
- Could compare with patients treated with same drugs at equivalent doses.

Summary

- **Evidence-based toxicology can be seen as part of a wider movement to reconsider how we use toxicogical information**
- **Needs to be proactive as well as reactive**
- **Toxicology needs to be thought as an integral part of medical and environmental research**
- **All options should be open**
- **Undoubtedly this will make regulation of levels more difficult at first but we get TDIs etc more realistic for human health**

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- MRC 3Rs Strategic funding

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