

Changes to ICHS2: Why are they needed, how will it help?

Genetic Toxicology Association

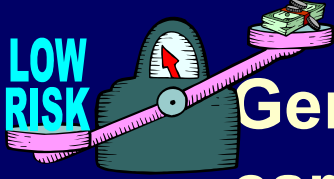
September 11rd , 2008



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CDER view of genotoxicity findings



Genotoxicity is seen only as a predictor of carcinogenicity prior to drug approval, most drugs will undergo carc testing but results not available until NDA submission. Many people (hundreds or thousands) including healthy volunteers will have been exposed to repeated, pharmacologically active drug doses.

- Reactions to positive findings may differ between clinical review divisions
- For clinical trials in patients, particularly for a serious indication, positive responses can be acceptable
- For healthy volunteers, risks must be minimal



Equivocally positive *in vitro* cytogenetics assay

Treatment (µg/mL)	S9 Activation	Treatment Time	Mean Mitotic Index	Aberrations Per Cell (Mean +/- SD)		Cells With Aberrations	
						Numerical (%)	Structural (%)
DMSO Test Article	-	4	14.6	0.005	±0.071	3.0	0.5
5	-	4	14.7	0.005	±0.071	1.5	0.5
30	-	4	14.1	0.000	±0.000	2.5	1.0
50	-	4	7.0	0.115	±0.651	4.0	6.0**
MMC, 0.2	-	4	12.4	0.200	±0.530	3.0	15.0**
DMSO Test Article	+	4	15.2	0.005	±0.071	3.5	0.5
20	+	4	13.0	0.010	±0.100	2.0	1.0
30	+	4	10.8	0.015	±0.122	3.0	1.5
40	+	4	7.1	0.015	±0.122	2.5	1.5
CP, 10	+	4	12.2	0.130	±0.366	2.5	12.0**



Pharmaceuticals positive in carcinogenicity studies

- One third of drugs in PDR have positive or equivocal carcinogenicity results.
- Of those that are positive, two-thirds are non-genotoxic carcinogens.
- Many of the noncarcinogens have positive results in in vitro mammalian cell assays.



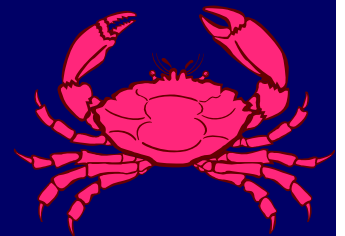
Challenges of Drug-Induced Tumorigenesis

- Drugs induce tumors by a variety of mechanisms unrelated to DNA damage
 - ◆ Exaggerated pharmacological effects
 - ◆ Immune suppression
 - ◆ Hormonal imbalance





Drug-induced tumors

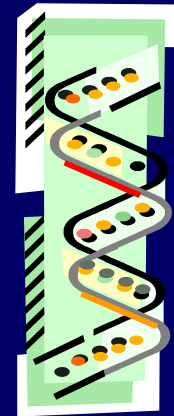


- **Haloperidol: blocks dopamine secretion, increases prolactin-- mammary tumors**
- **Omeprazole: increased stomach pH and gastrin secretion -- ECL(Enterochromaffin-like) tumors**
- **Sulfamethoxazole: decreases T3 and T4, increased TSH-- thyroid tumors**
- **Elidel: immunosuppression-- thymic lymphomas**
- **Finasteride: 5- α reductase inhibitor, increased LH-- Leydig cell tumors**



Challenges of Drug-Induced Tumorigenesis

- Drugs can induce tumors by a wide variety of mechanisms unrelated to DNA damage
- Some of these drugs have the occasional positive genetox response, probably unrelated to MOA
- The vast majority of those results come from in vitro mammalian cell assays.



Evaluation of the ability of a battery
of three in vitro genotoxicity tests to
discriminate rodent carcinogens
and non-carcinogens_ I. Sensitivity,
specificity and relative predictivity

David Kirkland, Marilyn Aardema, Leigh
Henderson and Lutz Müller

Mutation Research, 584, 1-256 (2005)



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Summary performance of individual in vitro assays in detecting rodent carcinogens

	Ames	MLA	MN	CA
No. of carcinogens tested in each test system	541	245	89	352
No. of clear positives ^a	318	179	70	231
Sensitivity (%)	318/541 (58.8%)	179/245 (73.1%)	70/89 (78.7%)	231/352 (65.6%)
No. of equivocal results	8	19	2	14
Sensitivity (%) if equivocal results counted positive	326/541 (60.3%)	198/245 (80.8%)	72/89 (80.9%)	245/352 (69.6%)



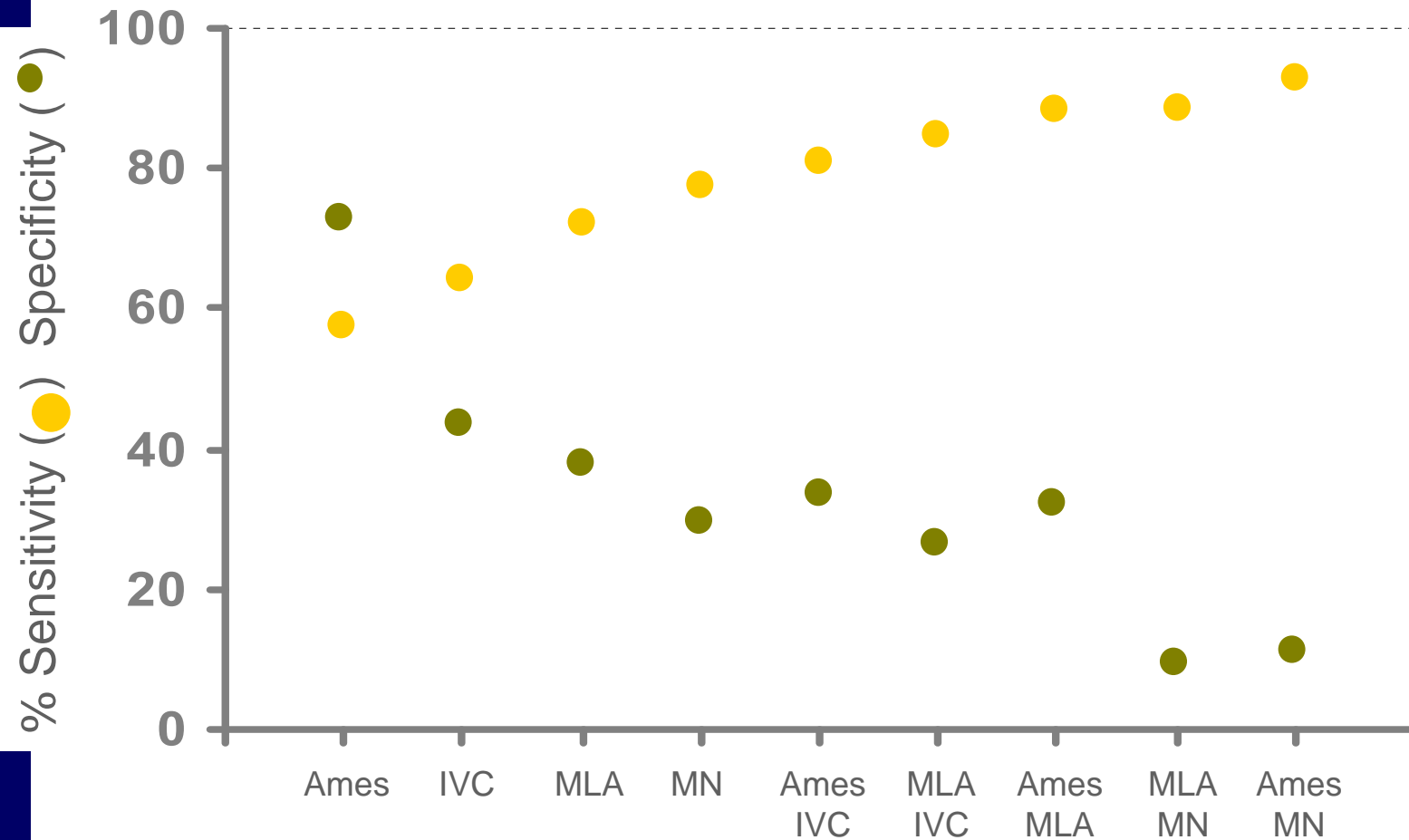
Summary performance of individual in vitro assays in detecting rodent non-carcinogens

	Ames	MLA	MN	CA
No. of non-carcinogens tested in each test system	176	105	26	136
No. of clear negatives	130	41	8	61
Specificity (%)	130/176 (73.9%)	41/105 (39.0%)	8/26 (30.8%)	61/136 (44.9%)
No. of equivocal results	6	9	6	4
Specificity (%) if equivocal results counted negative	136/176 (77.3%)	50/105 (47.6%)	14/26 (53.8%)	75/136 (55.1%)



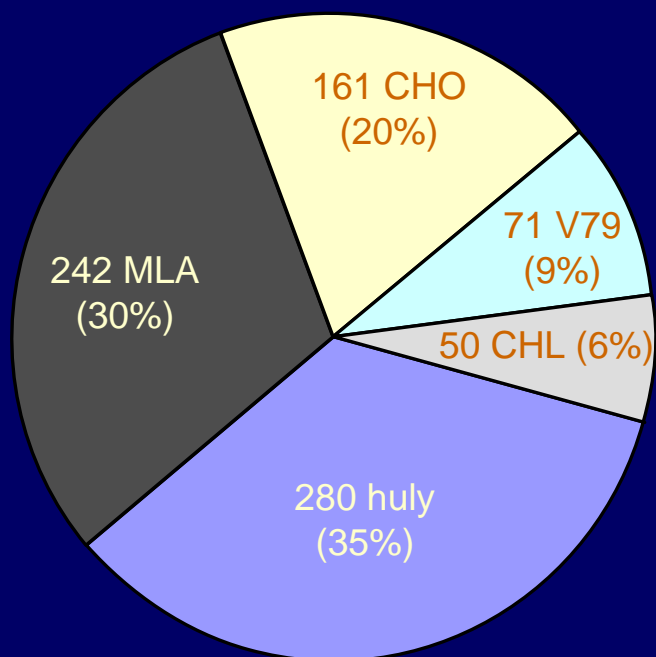
Specificity of test batteries

Kirkland et al, (2005). Mutat. Res. 584 (1-2), 1-256.



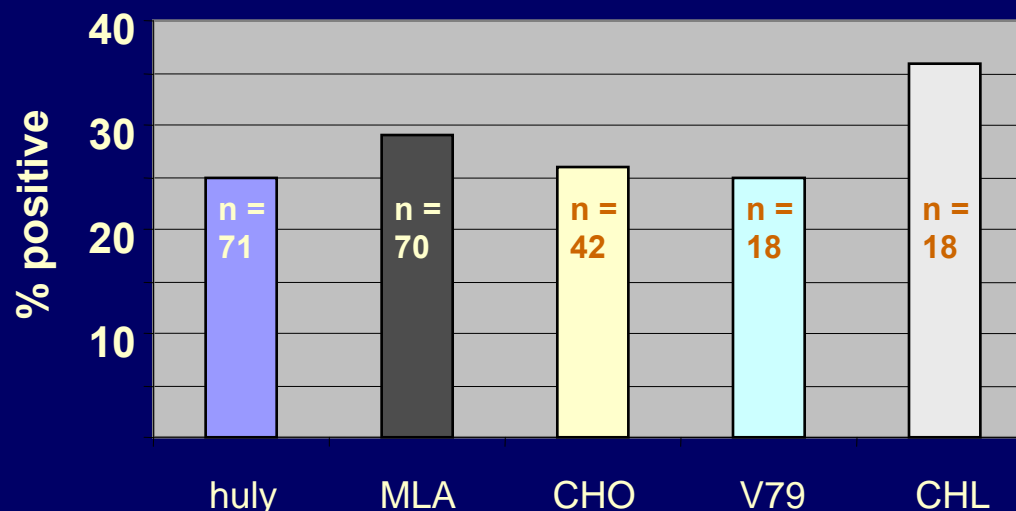
Mammalian cell assays: Use in regulatory testing and rates of positives

Data kindly provided by Peter Kasper, BfArM



**804 mammalian cell studies
submitted between 1995 and 2005**
(testing of 596 compounds)

Comparison of rate of positives
among the cell systems currently in use



219 of 804 studies positive = 27%
**181 of 596 compounds positive in
at least 1 in vitro clastogenicity test = 30%**



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The in vitro mammalian cell assays have high sensitivity because of the high frequency of positive responses (~25-30%). Therefore they get “credit” for identifying nongenotoxic carcinogens. In essence these are false positives because while the drugs turn out to be carcinogens, it is by another MOA.

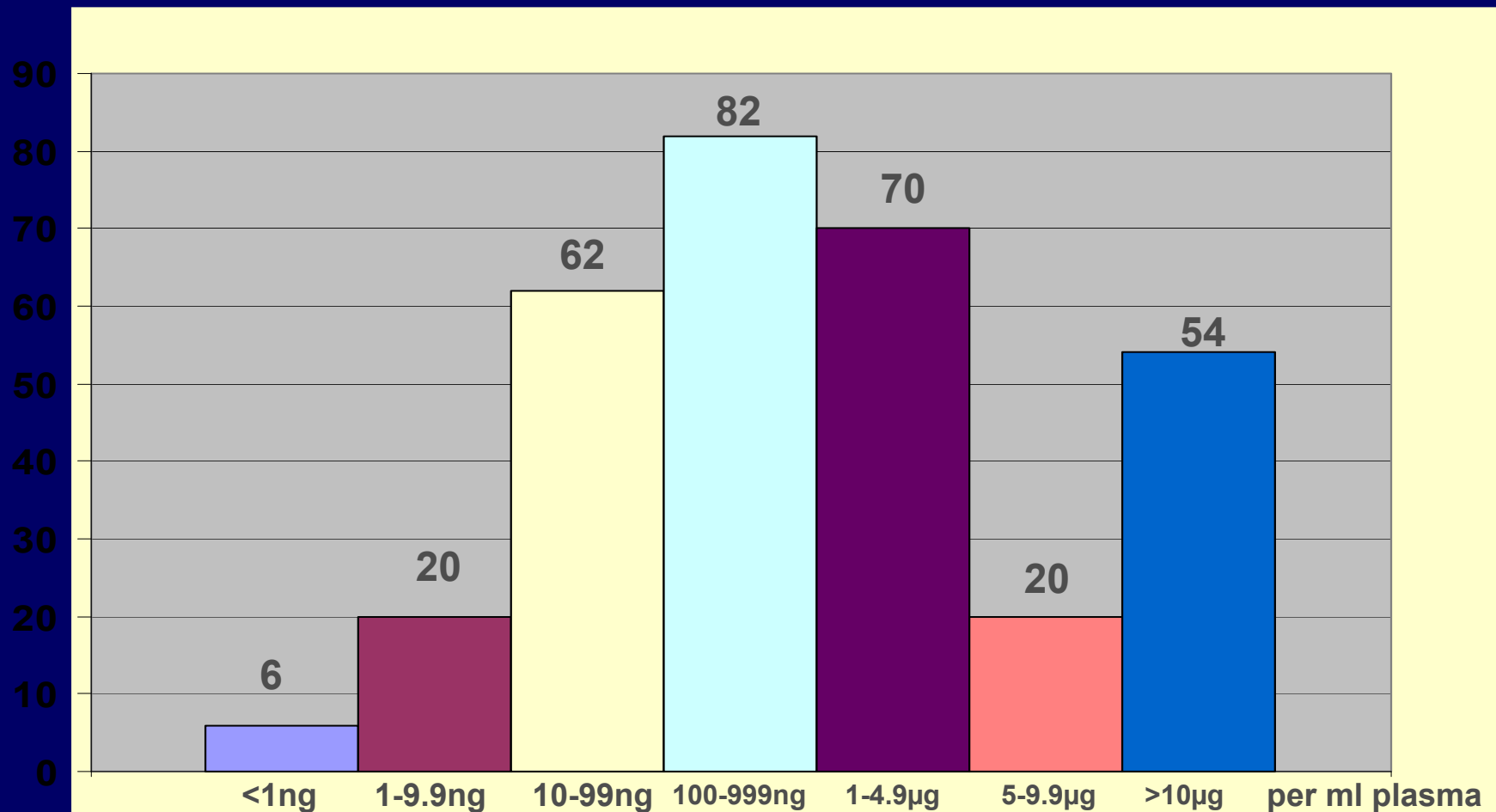


Changes to top concentration

- Current requirement is 10mM or 5 mg/ml.
- How do these concentrations relate clinical exposures?



Maximal concentrations of pharmaceuticals at steady state in blood/plasma (314 drugs according to Goodman&Gilman's, The pharmacological basis of therapeutics, 10th Edition, 2002)



ICH

Revisions to genotoxicity test guidelines, S2

Proposed revisions



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**Bacterial mutation assay
negative**

Option 1

Option 2

In vitro mammalian cell test

No in vitro mammalian cell test

a

b

**Negative
(or Positive
but not
relevant based
on WoE)**

Positive and relevant

either

MNT

integrated in toxicology study
Acceptable only if top dose
is appropriate

2nd end-point/tissue
+ integrated if possible

No 2nd in vivo

**If top dose is not acceptable
for genotoxicity evaluation**

or

**Acute genotoxicity
Assay (2 endpoints if possible)**

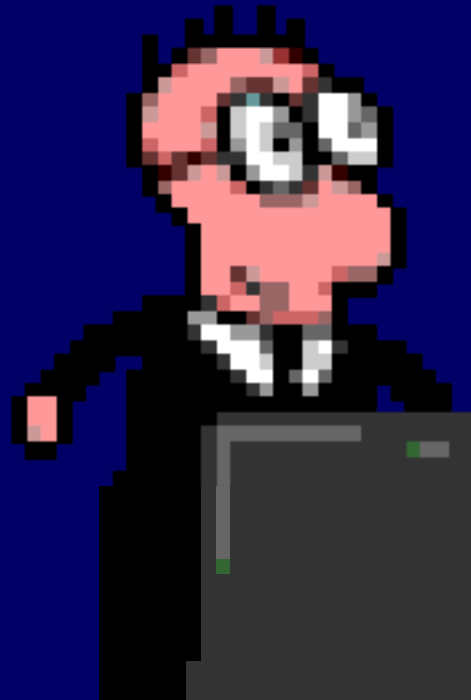
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How will this play out?

- Pharma currently screens drug candidates very early in development in nonGLP studies.
- Most use Ames assay and in vitro micronucleus assay. Positives generally discarded.
- For regulatory submission they will perform GLP Ames test and in vitro micronucleus assay since they already know the answer.
- Patient safety will be maintained but many fewer delays in development because of irrelevant positive results!



Thank you for your attention!



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