

# Consortium for the Investigation of Genotoxicity of Aromatic Amines

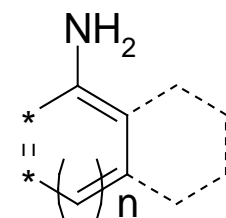
*Lhasa Ltd, International Collaborative Group Meeting, 16 May 2012*

# Aromatic Amines (AA)

## Why Aromatic Amines ??

- Ubiquitous in drugs, materials and foods
  - Prim. AA's in 89 drugs and 131 clinical study cpds [Bentzien, 2010]
  - Textiles, leather, plastics, cosmetics, cooked meat, etc.
- Many strong mutagens/carcinogens known
  - But an equally large number is innocuous
- Mutagenic mechanisms are well explored
  - The aromatic amines are one of the chemical classes in which the structural and molecular basis of carcinogenicity is most clearly understood.<sup>5</sup> This
- Most frequent class of genotoxic functional group
  - Structural alerts not sufficient for mutagenic classification
  - Many molecular properties have been correlated
  - Contradictory findings in QSAR studies

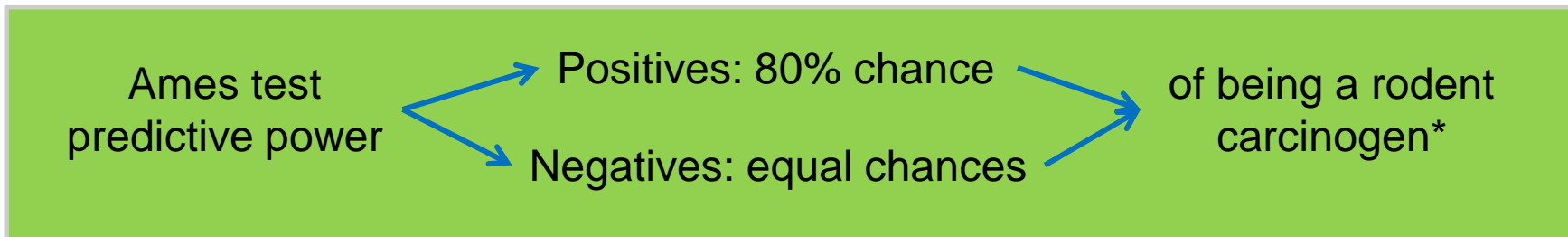
*Benigni, Chem Rev. 2000, 100, 3697.*



n = 1, 2

# Relevance of Ames Test

Genetically engineered *Salmonella typhimurium* strains



*Benigni, Ann Ist Super Sanita 2008, 44, 48.*

**\*Highly predictive of human carcinogen (80%)**

Table 2. Carcinogenicity prediction by STTs in a NTP comparative exercise.

*NTP study: Zeiger, Environ Mol Mutagen 1990, 16, 1.*

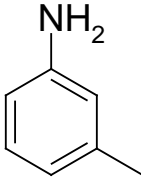
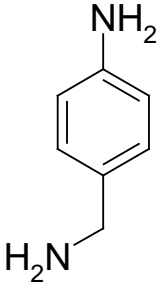
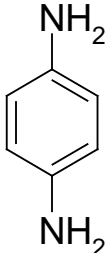
	Chi-square (p values)
<i>STT</i>	
Ames test	< 0.0001
Chromosomal aberrations (CHO cells)	0.011
SCE (CHO cells)	0.277
Mouse lymphoma cells mutation	0.305

*Benigni, Exp Opin Drug Metab Toxicol 2010, 6, 809.*

SCE – sister chromatid exchange

# Contradictory Ames Results

## Influence of purity levels

			
<b><u>Ames results</u></b>			
- S9	Pos	Neg	--
+ S9	Pos	Pos	Pos*
Re-purified			
- S9	Neg	Neg	Neg**
+ S9	Neg	Neg	Neg**
	GSK	Nicolette, IIRUSA Conference, Dec '08	Burnett, Mutat Res. 1982, 103, 1.

\* aged in DMSO  
\*\* freshly prepared

# Genotoxicity of Aromatic Amines

## Pharma-wide Consortium

- Initiated Feb 2011 by Royal Society of Chemistry and Pfizer
  - AZ and GSK had started Ames data exchange independently in 2009
- First mtg with AZ, Merck Co, Eli Lilly, Novartis, GSK; coordinated by Lhasa
- **Remit: to collect, model and publish Ames test data for aromatic amines**
- Major obstacles and their solutions
  - **Diversity of Ames test protocols** → Accept data from any Ames protocol
  - **Large variation in numbers of cpds tested by each company** → Limit first stage of data exchange to 25 cpds per company
  - **IP issues** for data sharing → Focus on cpds with MW < 200 and in public domain (CAS number)

# Genotoxicity of Aromatic Amines

## Consortium Progress

- Dec 2011: data exchange of structural identifiers
  - **179 primary aromatic amines**
  - Blind modelling of Ames predictions by some companies
- Jan 2012: data exchange of Ames test results
  - **ca. 2/3 of molecules are Ames-negative**
- May 2012: first draft of collaborative publication
  - Individual Ames results will be on hold for 18 months
- Next stage of collaboration:
  - Several other pharma companies are joining
  - Exchange more Ames results; test/re-test more AA's
  - Lhasa to improve Derek's AA alerts

# Learnings

## Consortium potential and pitfalls

- Prerequisite: mind shift within the pharma industry
  - Ames data (and many others) not considered proprietary material any longer
  - Collaborative research is the new working model
- Critical mass of committed individuals is crucial
  - .... as is buy-in of leadership
- Clear remit
  - Impose constraints to speed up the process
- Regular but flexible meetings
  - Agendas, mtg minutes, updates maintain momentum
- How do we tackle the data diversity/integrity ?

# Acknowledgements

## Chemists, toxicologists, scientists at

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- Novartis
- Bayer Healthcare
- Hoffmann-La Roche
- Janssen R&D
- Abbott
- Sanofi