

## **SYMPOSIUM**

**“Occupation, Aromatic Amines,  
Polycyclic Aromatic Hydrocarbons  
and Bladder Cancer”**



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## **“Exposure to Aromatic Amines - Overview on Chemistry, Biotransformation and Possible Modes of Action”**

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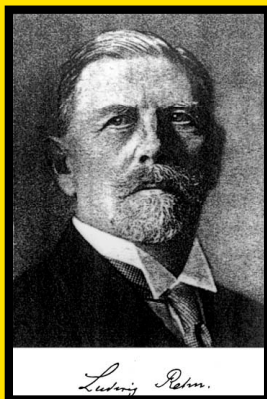
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**BGFA, 09 November 2009, Bochum, Germany**

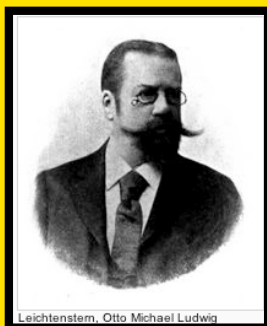


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## History



1895 L. Rehn, Blasengeschwülste  
bei Fuchsin-Arbeitern.  
Arch. Klin. Chir.  
50, 588-600.



1898 O. Leichtenstern,  
Harnblasenentzündung und  
Harnblasengeschwülste bei  
Arbeitern in Farbfabriken.  
Dtsch. Med. Wochenschr.  
24, 709 ff.

**Bladder cancer associated  
with aromatic amines**

1895 Anilin (?)

1898 2-Naphthylamine

1906 Benzidin

1955 4-Aminobiphenyl



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# Exposure of Aromatic Amines to Humans

## General Population

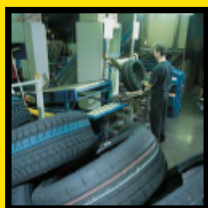


1. Diet (e.g. pesticides)
2. Pharmaceuticals (e.g. prilocain → o-toluidine)
3. Hair dyes
4. Smoking (active and passive [ETS])
5. Diesel engine exhaust



There is a long-term exposure for low-levels of aromatic amines in non-smokers

## Workplace



6. Occupational exposure  
(e.g. rubber, textile, dye industries etc.)

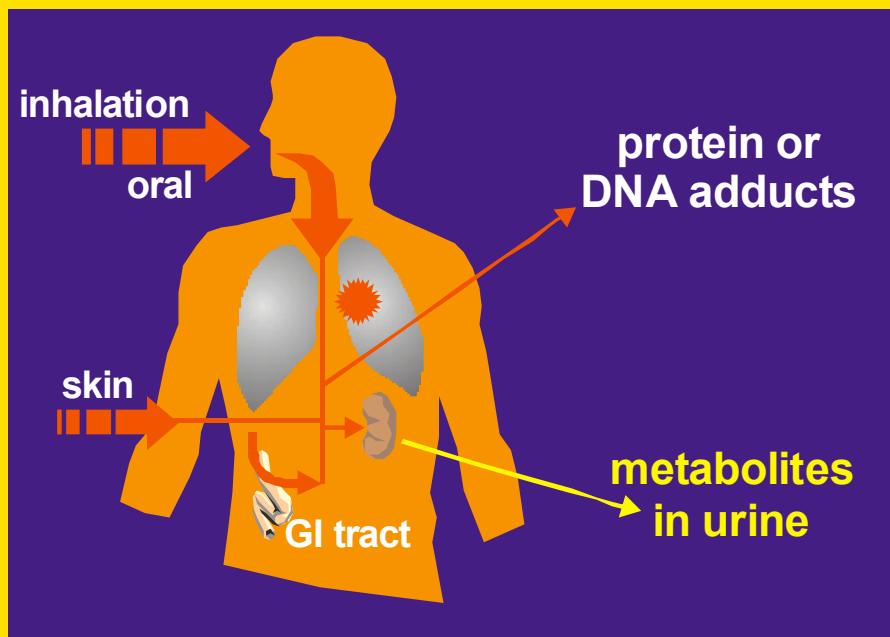


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## Exposure Routes - Organotropism of Cancer Induced by Aromatic Amines

### Exposure pathways

### Biomarkers



### Humans

bladder  
pancreas  
larynx

### Experimental animals

liver  
bladder  
kidney  
& others organs

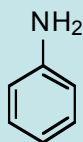
### Today

- Bladder cancer represents about 7% of human malignancies
- Bladder cancer is the third most prevalent cancer type in men 60 years and older

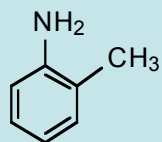


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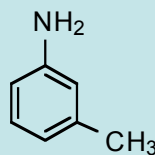
## Structures of Aromatic Amines



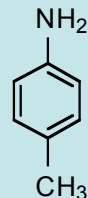
**Aniline**



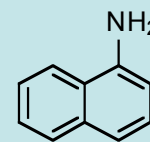
**o-Toluidine (1)**



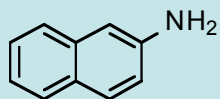
**m-Toluidine**



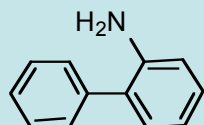
**p-Toluidine**



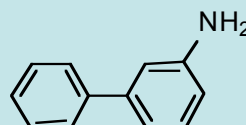
**α-Naphthylamine**



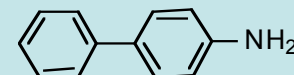
**β-Naphthylamine (1)**



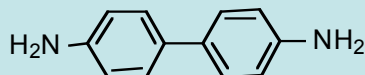
**2-Aminobiphenyl**



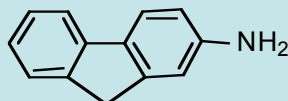
**3-Aminobiphenyl**



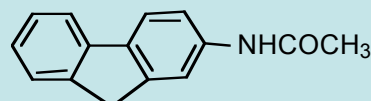
**4-Aminobiphenyl (1)**



**Benzidine (1)**



**2-Aminofluorene**



**N-Acetylaminofluorene**

(1) IARC/WHO  
Classified in Group 1  
„Human Carcinogen“

MAK III  
Kategorie 1+2  
„Human Carcinogen“

Aromatic amines account for 12% of the 415 chemicals that are either known or strongly suspected to be carcinogenic in humans U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program (2005) 11th Report on Carcinogens, National Toxicology Program, Research Triangle Park, NC



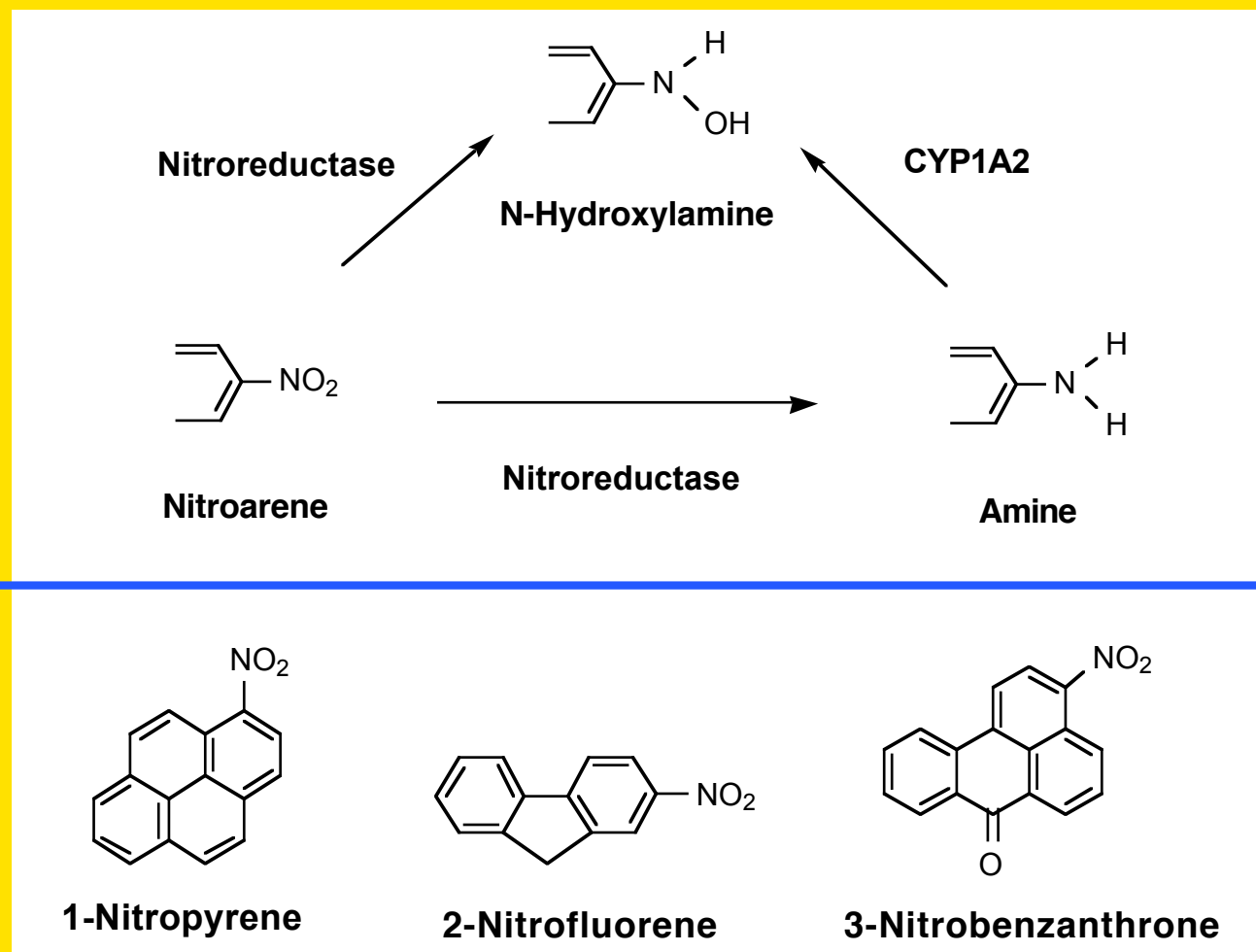
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## Activation of Nitroarenes via Aromatic Amines

### Nitroreduction

Liver,  
Extrahepatic  
tissues,  
Intestinal  
bacteria

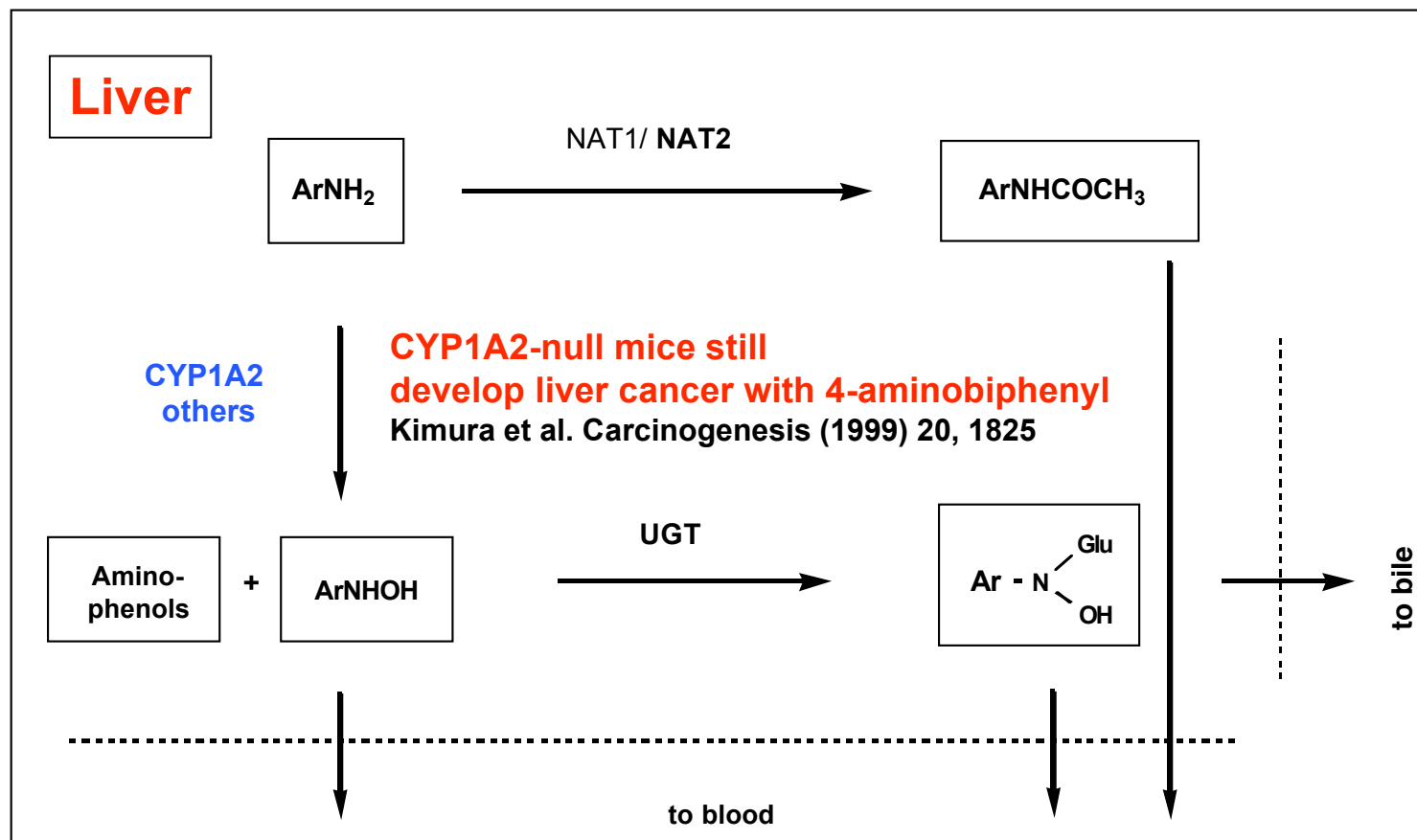
Diesel exhaust





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## Metabolism of Aromatic Amines in Liver (I)



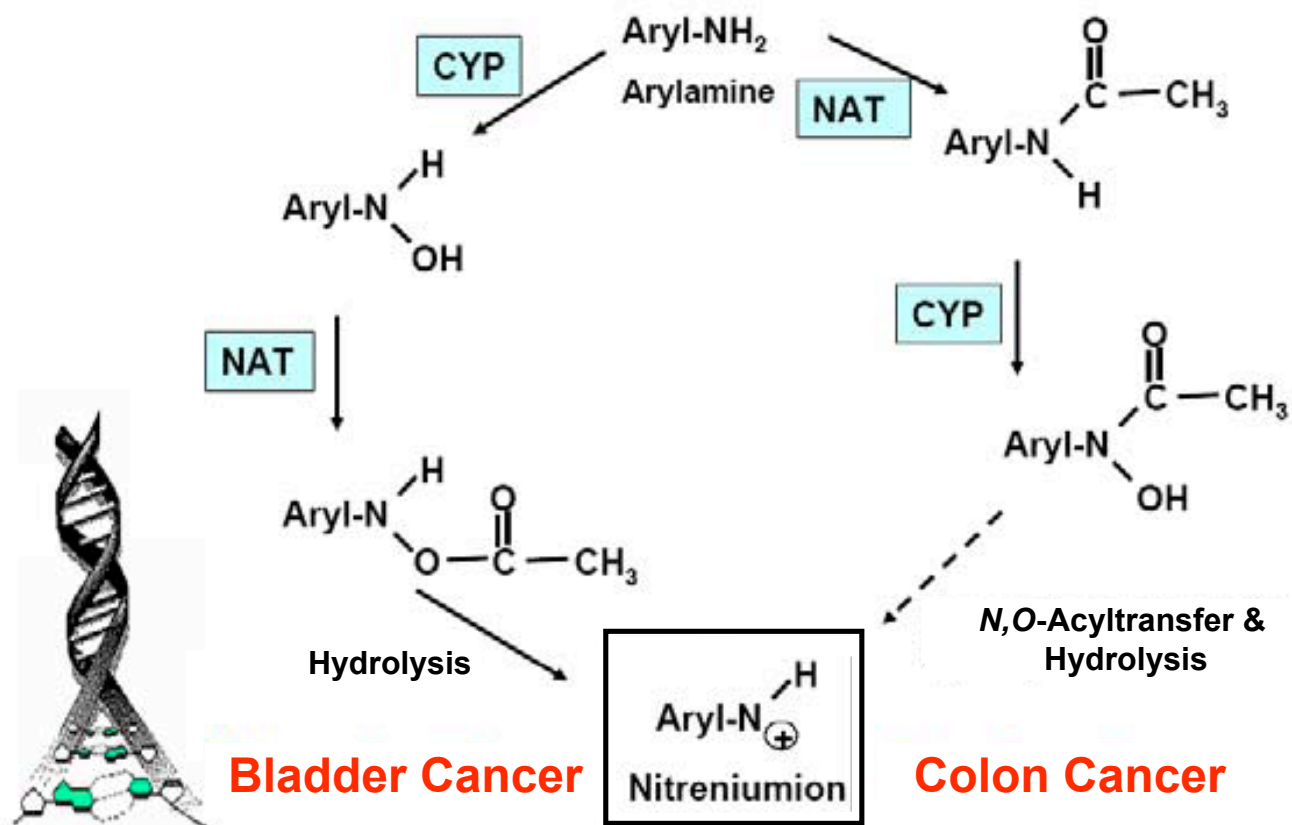


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## Metabolism of Aromatic Amines in Liver (II)

### Slow acetylators

### Fast acetylators

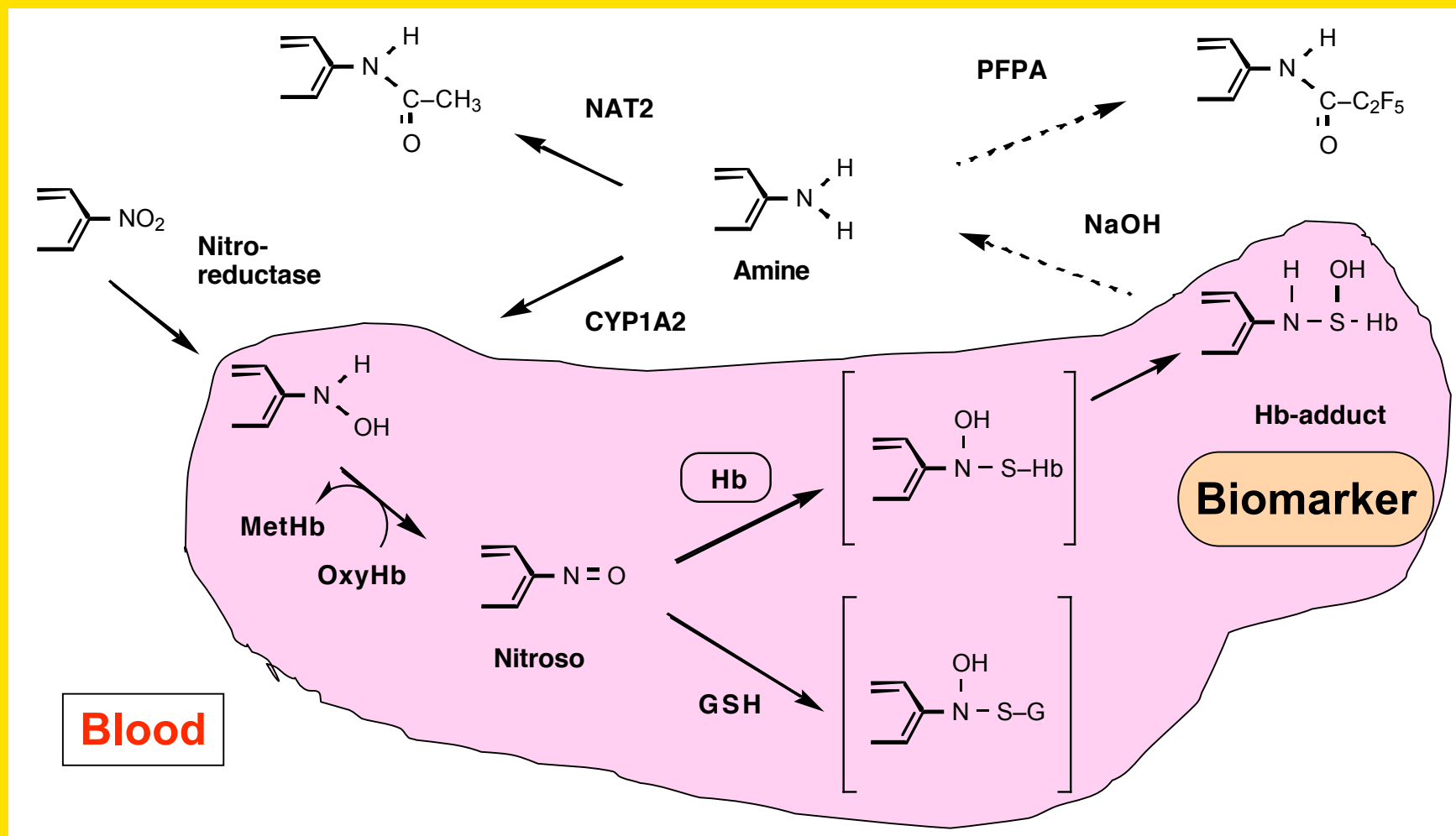


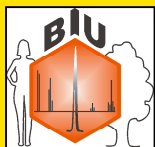




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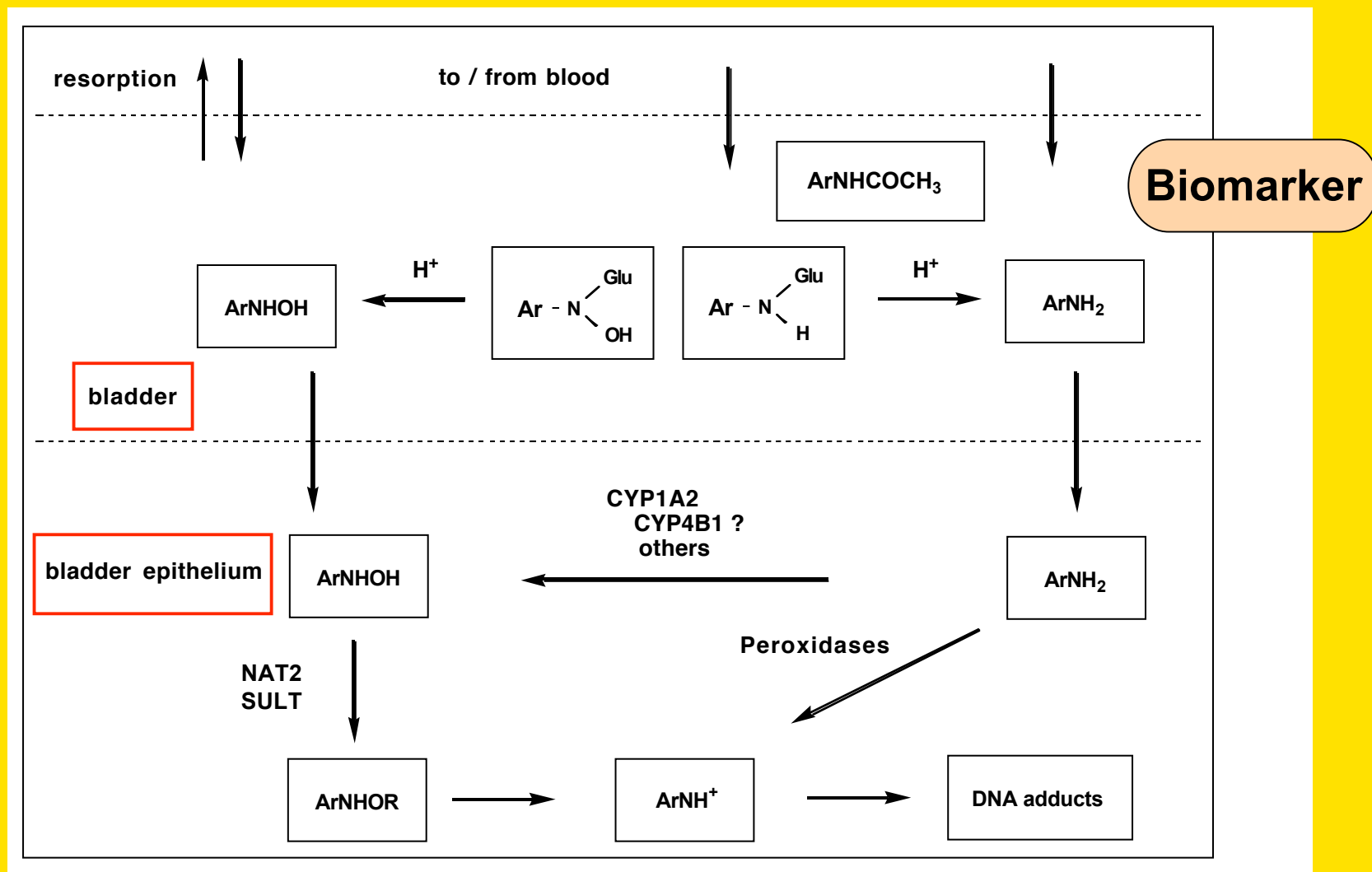
## Formation of Hb Adducts of Aromatic Amines





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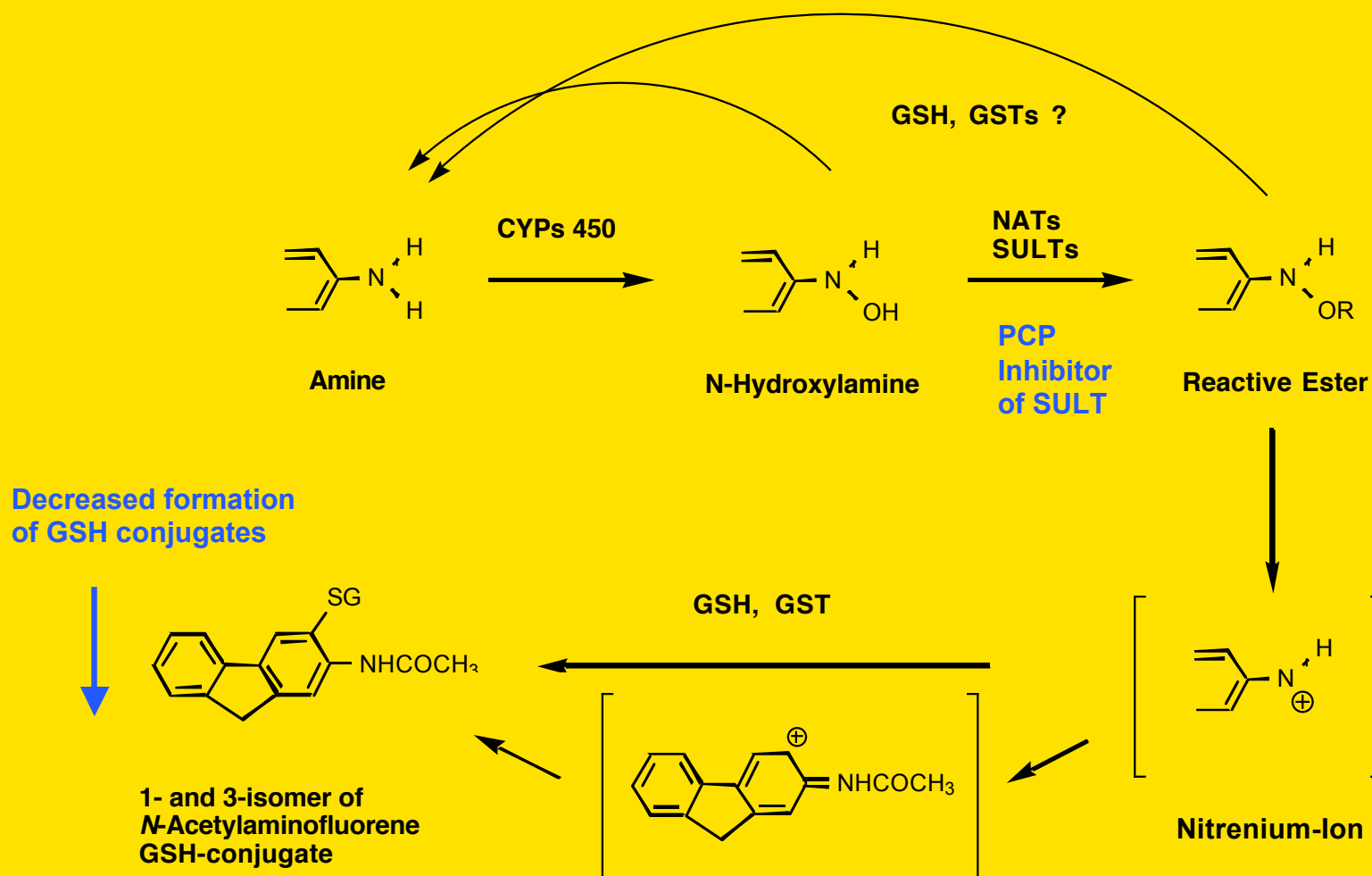
## Metabolism of Aromatic Amines in Bladder Epithelium





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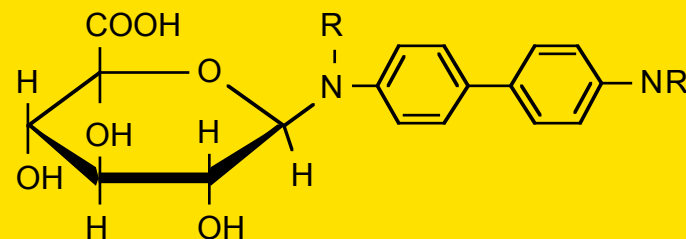
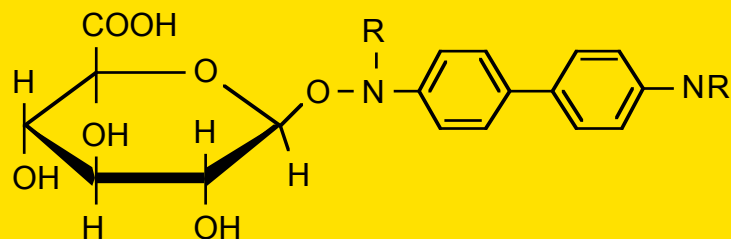
## The Role of Gluthathione in Detoxication of Reactive Intermediates of Arylamines





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## Glucuronidation of different benzidine, benzidine metabolites, and 4-aminobiphenyl



R = H, -COCH<sub>3</sub>

Substrate	UGT1A1	UGT1A4	UGT1A6	UGT1A9	UGT2B7
Benzidine	18 ± 2	1114 ± 36	220 ± 40	1327 ± 60	150 ± 17
N-Acetylbenzidine	21 ± 5	889 ± 84	N D	1193 ± 13	123 ± 3
N'-Hydroxy-N-acetylbenzidine	11 ± 1	1417 ± 6	N D	633 ± 47	137 ± 7
N-Hydroxy-N-acetylbenzidine	11 ± 1	997 ± 42	400 ± 40	9667 ± 600	170 ± 3
N-Hydroxy-N,N'-diacetylbenzidine	87 ± 1	240 ± 24	280 ± 20	38 467 ± 1270	187 ± 10
4-aminobiphenyl	22 ± 1	628 ± 60	N D	5133 ± 213	163 ± 7

Values are expressed as pmol / 2h / mg protein and represent means ± SEM for triplicate determinations.

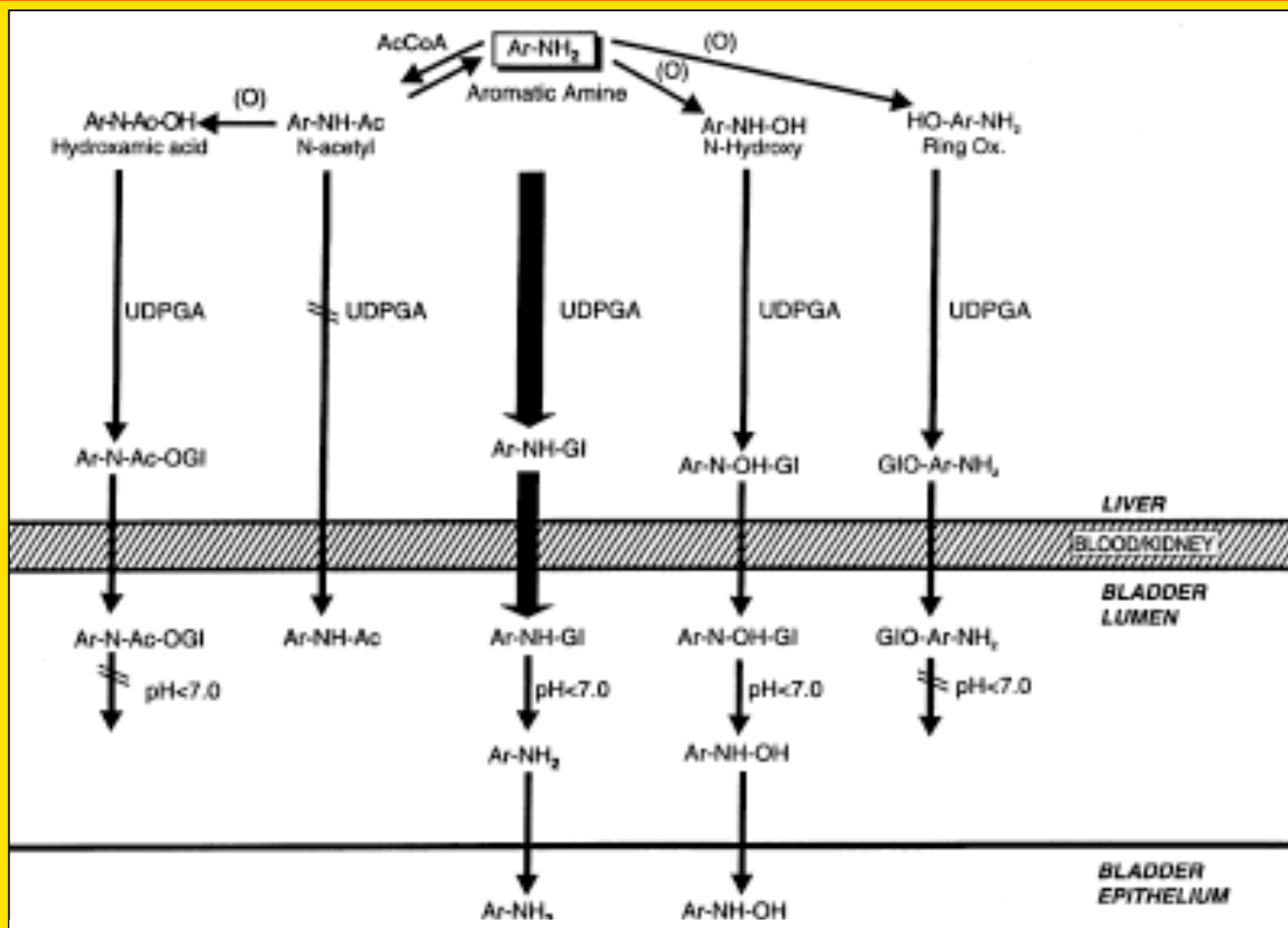
Ciotti et al. Carcinogenesis, 20, 1963 (1999)



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# Pathways of Aromatic Amine Metabolism

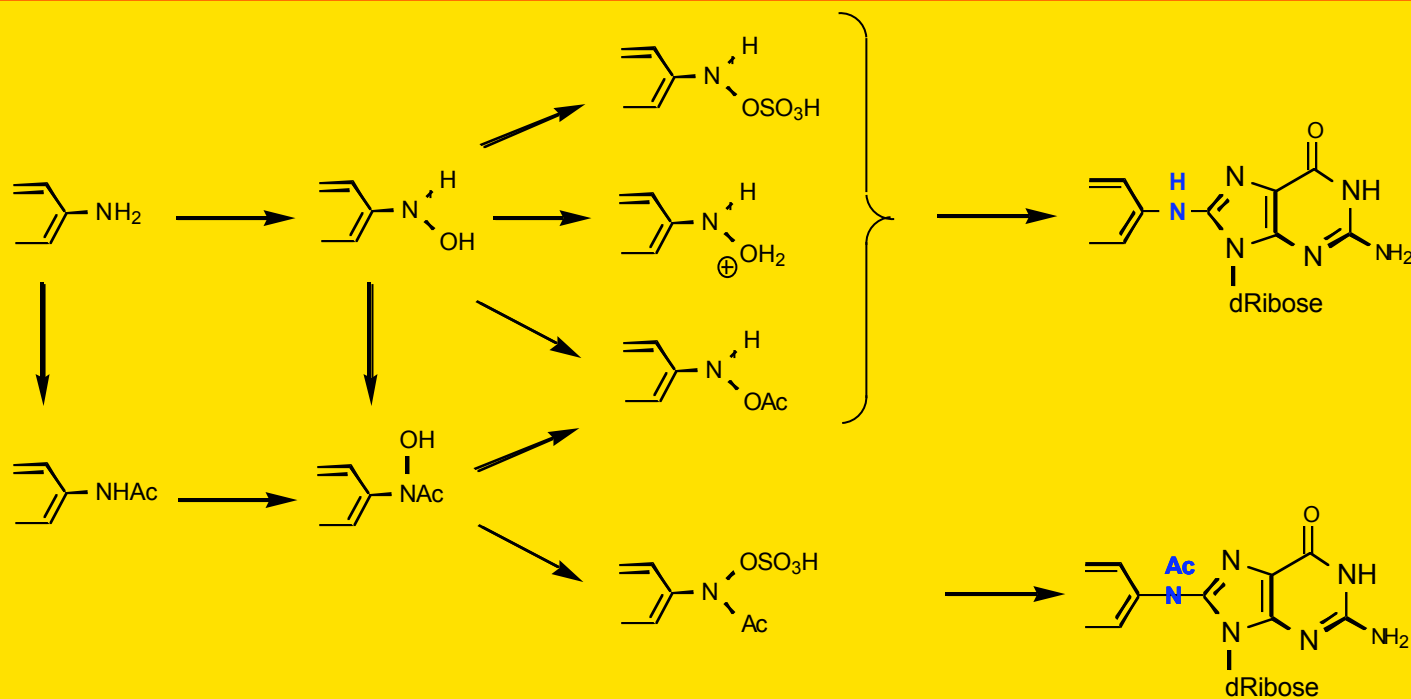
(Ciotti et al. Carcinogenesis (1999) 20, 1963)





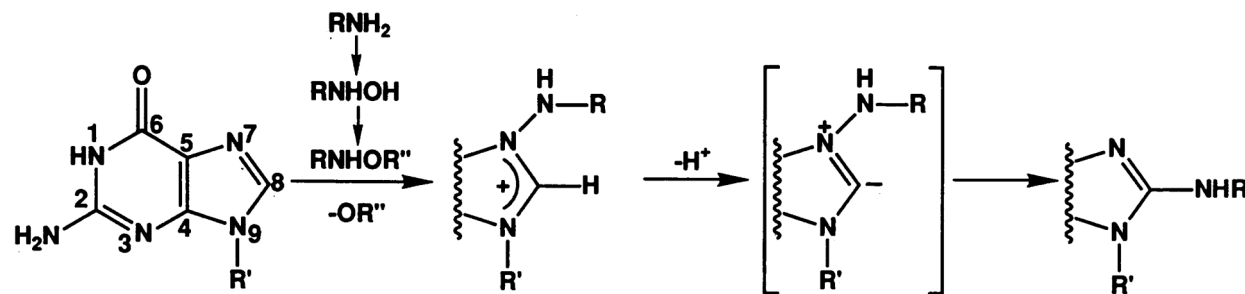
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# Formation of C8-dG Adducts of Arylamines



Reactive Intermediates

Humphreys et al. PNAS,  
(1989) 89, 8278

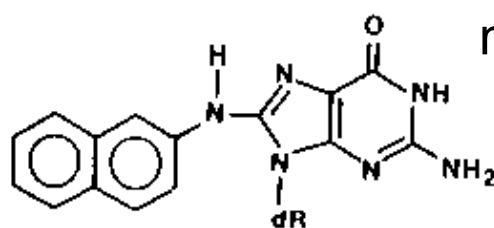




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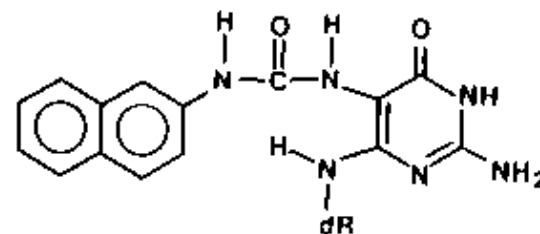
## DNA Adducts of 2-Aminonaphthalene

DNA adducts  
in liver and  
urothelium  
of dogs

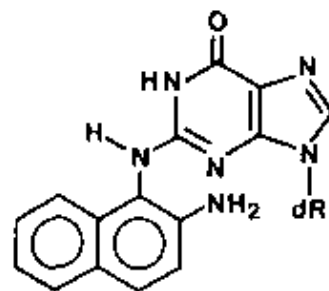


N-(deoxyguanosin-8-yl)-2-NA

major

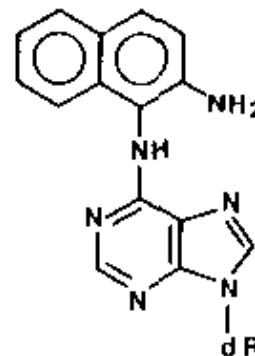


Ring-opened N-(deoxyguanosin-8-yl)-2-NA



1-(deoxyguanosin-N<sup>2</sup>-yl)-2-NA

minor



1-(deoxyadenosin-N<sup>6</sup>-yl)-2-NA

minor

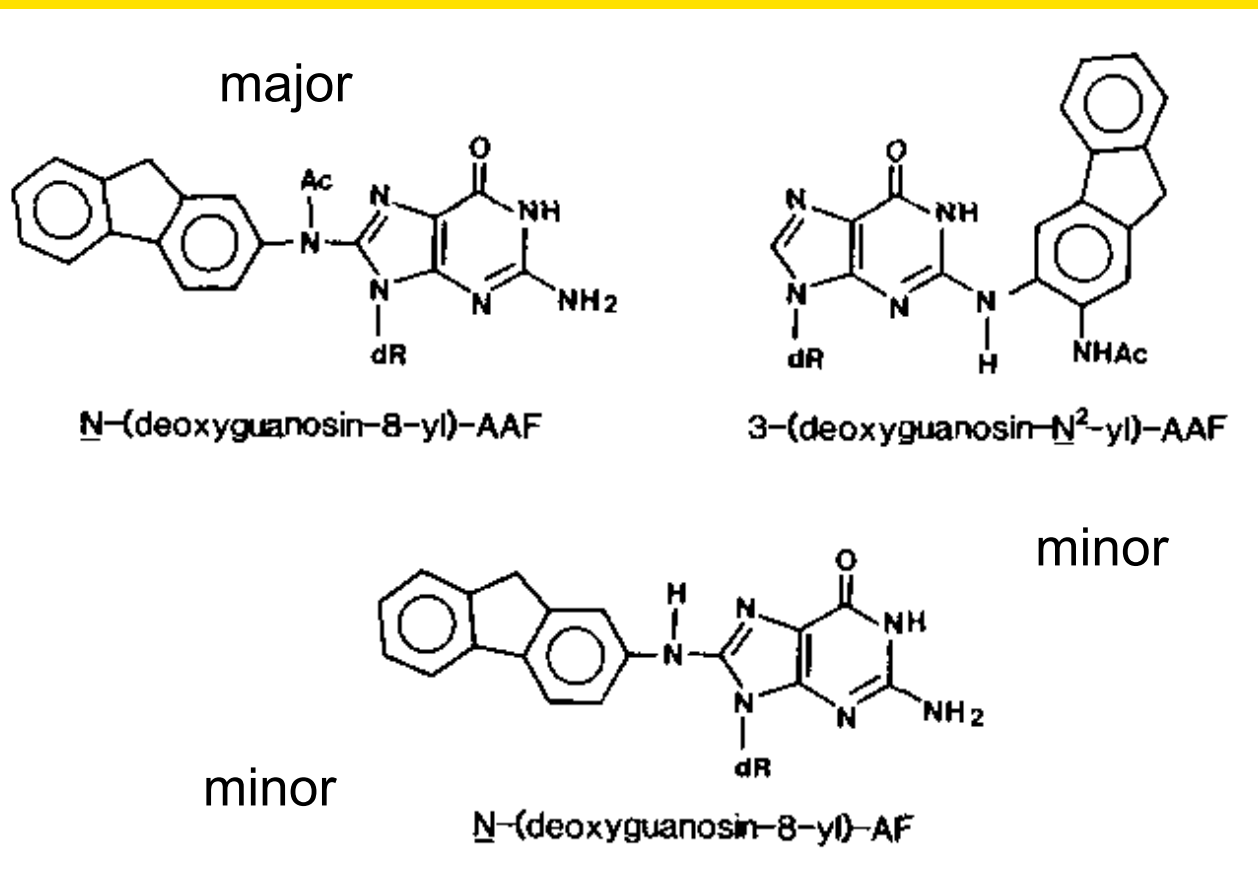
Beland & Kadlubar, EHP, 62, 19 (1985)



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## DNA Adducts of 2-Acetylaminofluorene

DNA adducts  
in liver  
of rats



Beland & Kadlubar , EHP, 62, 19 (1985)

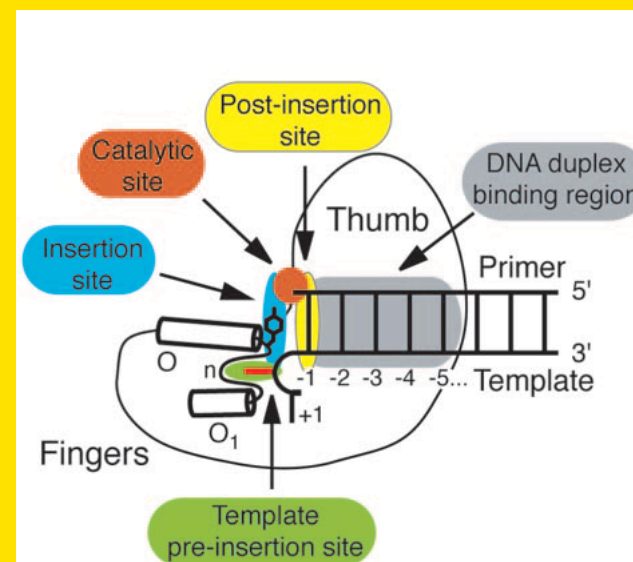
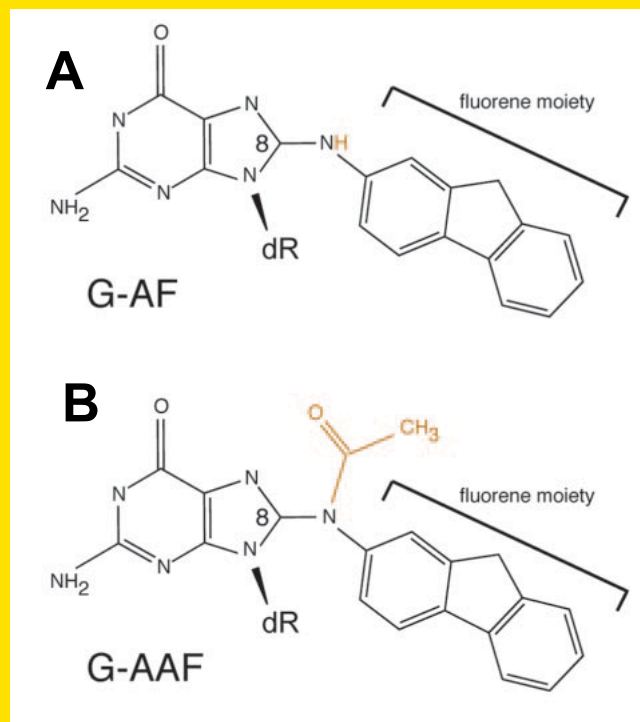




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## Translesion Synthesis of Aromatic Amine DNA Adducts By a High-Fidelity DNA Polymerase

Hsu et al. J Biol Chem (2004) 279, 50280-85



*Bacillus*  
DNA Pol I  
fragment

- A. Induced slow translesional synthesis.**
- B. Blocks replication - replaced by a specialized lesion bypass polymerase (Y family Pol) allowing translesional synthesis. Translesional synthesis can lead to mutations (e.g. G to T transversions)**



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## Conclusions

- **A substantial knowledge has been obtained regarding metabolism of aromatic amines and the DNA interaction of their reactive intermediates.**
- **However, further investigations are still required to better understand the mechanisms responsible for the organotropism of carcinogenic aromatic amines. In particular, studies regarding the interplay of genetic disposition, genotoxic and non-genotoxic effects are of interest.**





# Thank you for your attention!

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