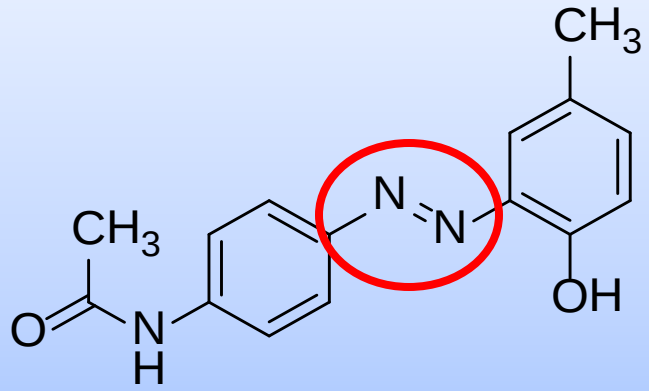
Evidence on the Carcinogenicity of C.I. Disperse Yellow 3

January 25, 2013

Meeting of the Carcinogen Identification Committee

Cancer Toxicology and Epidemiology Section
Reproductive and Cancer Hazard Assessment Branch

Identity of C.I. Disperse Yellow 3



CAS-RN: 2832-40-8

- Molecular Formula: $C_{15}H_{15}N_3O_2$
- Molecular Weight: 269.30
- Chemical Class: monoazo dye
- Chemical Appearance: powder
- Water Solubility: 1.18 mg/L (at 25°C)

C.I. Disperse Yellow 3 Uses

- A textile dye for coloring nylon, polyvinyl chloride and acrylic fibers, wools, furs, cellulose acetate, polystyrene, and other thermoplastics
- Products include clothing, hosiery, and carpeting
- Dyes in ink products, and in pulp and paper manufacture

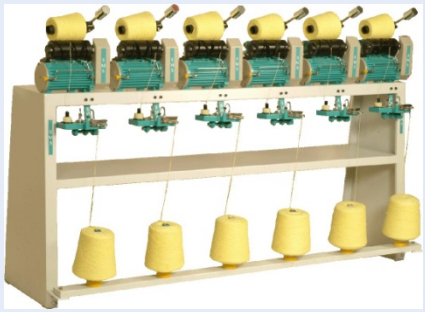
Occurrence of C.I. Disperse Yellow 3

- Primarily used in dyeing of synthetic textiles such as yarns, fabrics, and carpets.
- Populations potentially exposed:
  - Workers in synthetic textile manufacturing
    - Example: is one of 39 disperse dyes known to cause contact allergic dermatitis in textile workers.
  - General public using synthetic textiles
    - Example: allergic eczema is associated with nylon hosiery containing C.I. Disperse Yellow 3.

CI Disperse Yellow 3 at various concentrations on polyester fabric

Potential Exposures to C.I. Disperse Yellow 3 in Textile Manufacturing

- Dyeing with C.I. Disperse Yellow 3
  - Yarn stage
    - Batch dyeing machines.
  - Fabric/carpet stage
    - Continuous and batch dyeing machines.
- Handling of dyed yarns, fabrics, and carpets.
  - Exposure to CI DY3 (dermal and respiratory) may be more likely in handling than in dyeing.



Carcinogenicity Studies in Humans

- There are no epidemiology studies of humans with *documented exposure* to C.I. Disperse Yellow 3.
- There are four epidemiology studies of textile workers with *potential exposure*.
  - All four studies were of bladder cancer only.
  - All four were case-control design.
  - Three were conducted in Spain, one in New Zealand.
  - All four used interviewer-administered questionnaires to collect exposure data
  - All four used standard occupation/industry coding. One (Serra et al. 2008) additionally used detailed questions about the textile manufacturing workplace.

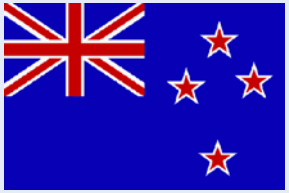
Epidemiology study: Gonzales *et al*., 1988

- Case-control study in Spain.
  - Incident cases from one hospital.
  - Deceased cases from a local death registry.
- 57 bladder cancer cases identified 1978 -1981.
- 107 hospital and deceased controls
- ***"Textile dyeing or printing"*** **OR=4.41, 95% CI= 1.15-16.84**, based on 8 exposed cases and 3 exposed controls.
- **C.I. Disperse Yellow 3 was among 72 dyes mentioned in article.**
- Limitation: most subjects deceased (75%) by time of interview, requiring proxy interview (e.g. with spouse).

Epidemiology study: Gonzales *et al*., 1989

- Case-control study in Spain
  - Incident cases from 12 hospitals in four geographic regions.
- 497 bladder cancer cases (438 male & 59 female) occurred 1985 -1986.
- Two control groups
  - Hospital
  - General population.
- ***"Textile dyers"*** **OR=1.29, 95% CI= 0.5-3.1**, based on 11 exposed cases and 17 exposed controls.
- **C.I. Disperse Yellow 3 was not mentioned in the article.**

Epidemiology study: Dryson *et al.*, 2008



- Case-control study in New Zealand
  - Cases from nationwide cancer registry.
- 213 bladder cancer cases occurring 2003 -2004.
- 471 controls from general population.
- **"T*extile products machine operators - textile bleaching, <u>dyeing</u>, and cleaning*" OR=0.81, 95% CI=0.19-3.54**, based on three exposed cases and 10 exposed controls).
- **C.I. Disperse Yellow 3 was not mentioned in the article.**

Epidemiology study: Serra *et al.*, 2008

- Case-control design at 18 hospitals in Spain.
- 1,182 bladder cancers (1,065 male, 117 female) 1998-2001.
- 1,221 controls from the same hospitals.
- Interviewer-administered questionnaires with module designed specifically for textile industry.
- ***"Winding, warping, and sizing"* with "*synthetic*" materials** (**OR=15.39, 95% CI=1.89-125.29**, based on 11 exposed cases and 1 exposed control).
- ***"Synthetic"* materials 10+ years (OR=2.62, 95% CI 1.14-6.01**, based on 21 exposed cases and 9 exposed controls)
- **C.I. Disperse Yellow 3 was not mentioned in the article.**

Two Carcinogenicity Studies in Rats

- National Toxicology Program (NTP), 1982
- F344 rats (males, females)
  - 50 animals/sex/dose
  - 0, 5,000 or 10,000 ppm in feed for 103 weeks and terminated by 104 weeks.
- Liver and stomach tumors were observed in males

Feed Studies in Male F344 Rats

Organ	Tumor	Dose group (ppm)			Trend test *p* value
		0	5000	10000	
Liver	Hepatocellular adenoma	**1/31**	**15/45****	**10/39***	**<0.05**
	Combined hepatocellular adenoma and carcinoma	**2/31**	**15/45****	**11/39***	**<0.05**
Stomach	Glandular portion: Combined adenoma, mucinous adenocarcinoma, and sarcoma	**0/30**	**2/45**	**1/39**	**NS**
	Non-glandular portion: Combined squamous cell papilloma and fibrosarcoma	**0/30**	**2/45**	**0/39**	**NS**

Pairwise comparison with controls; * p<0.05, ** p<0.01

Feed Studies in Female F344 Rats

- **No treatment-related tumors were observed**

Two Carcinogenicity Studies in Mice

- National Toxicology Program (NTP), 1982
- B6C3F$_1$ mice (males, females)
  - 50 animals/sex/dose
  - 0, 2,500 or 5,000 ppm in feed for 103 weeks and terminated by 104 weeks.
- Lung tumors in males.
- Hematopoietic system and liver tumors in females.

Feed Studies in Male $B6C3F_1$ Mice

Organ	Tumor	Dose group (ppm)			Trend test *p* value
		0	2500	5000	
Lung	Alveolar/bronchiolar adenoma	2/47	6/42	9/46*	< 0.05
	Combined alveolar/bronchiolar adenoma and carcinoma	3/47	7/42	9/46#	< 0.05

Pairwise comparison with controls; * p<0.05, # p=0.055

Feed Studies in Female $B6C3F_1$ Mice

Organ	Tumor	Dose group (ppm)			Trend test *p* value
		0	2500	5000	
Hemato-poietic System	Malignant lymphoma	10/50	16/50	19/50*	< 0.05
	Combined malignant lymphoma and leukemia	10/50	17/50	20/50*	<0.05
Liver	Hepatocellular adenoma	0/50	6/47*	12/46**	<0.001
	Hepatocellular carcinoma	2/50	4/47	5/46	NS
	Combined hepatocellular adenoma and carcinoma	2/50	10/47*	17/46**	<0.001

Pairwise comparison with controls; * p<0.05, ** p<0.01

Genotoxicity in Non-mammalian Species

- *Salmonella* reverse mutations
  - Positive: TA 97, 98, 1537, 1538 strains (+/-S9), and 100 (+S9) strains
  - Negative: TA 100 (-S9) and 1535 (+/-S9) strains

- Chromosomal aberrations in Frog larvae
  - Positive
- Sex-linked recessive lethal mutations in *Drosophila*
  - Negative

In Vitro Genotoxicity in Mammalian Species

- **Mouse lymphoma forward mutations**
  - **Positive: 2 tests (+S9)**
  - **Negative: 3 tests (-S9)**
- ***S*ister chromatid exchange in CHO cells**
  - **Positive: 1 test (+S9), 1 test (-S9)**
  - **Negative: 1test (-S9)**
- **Chromosomal Aberrations in CHO cells**
  - **Negative (+/-S9)**
- **Unscheduled DNA synthesis in rat hepatocytes**
  - **Positive (-S9)**

In Vivo Genotoxicity in Mammalian Species

Negative

- Micronucleus induction in mouse bone marrow
- DNA damage in rat liver

In Vitro Cell Transformation

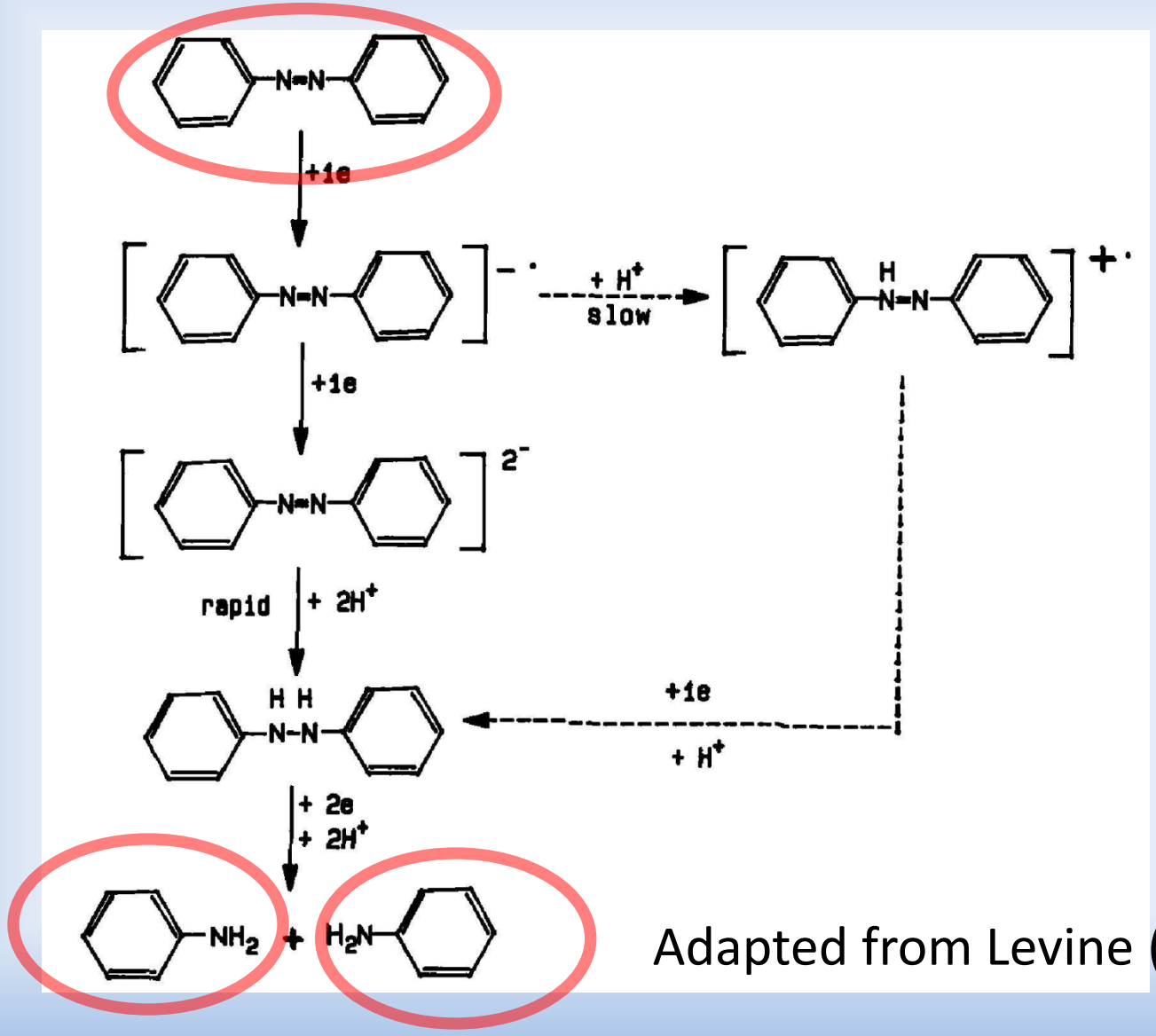
Negative

- BALB/c 3T3 mouse cells (-S9)

Pharmacokinetics and Metabolism

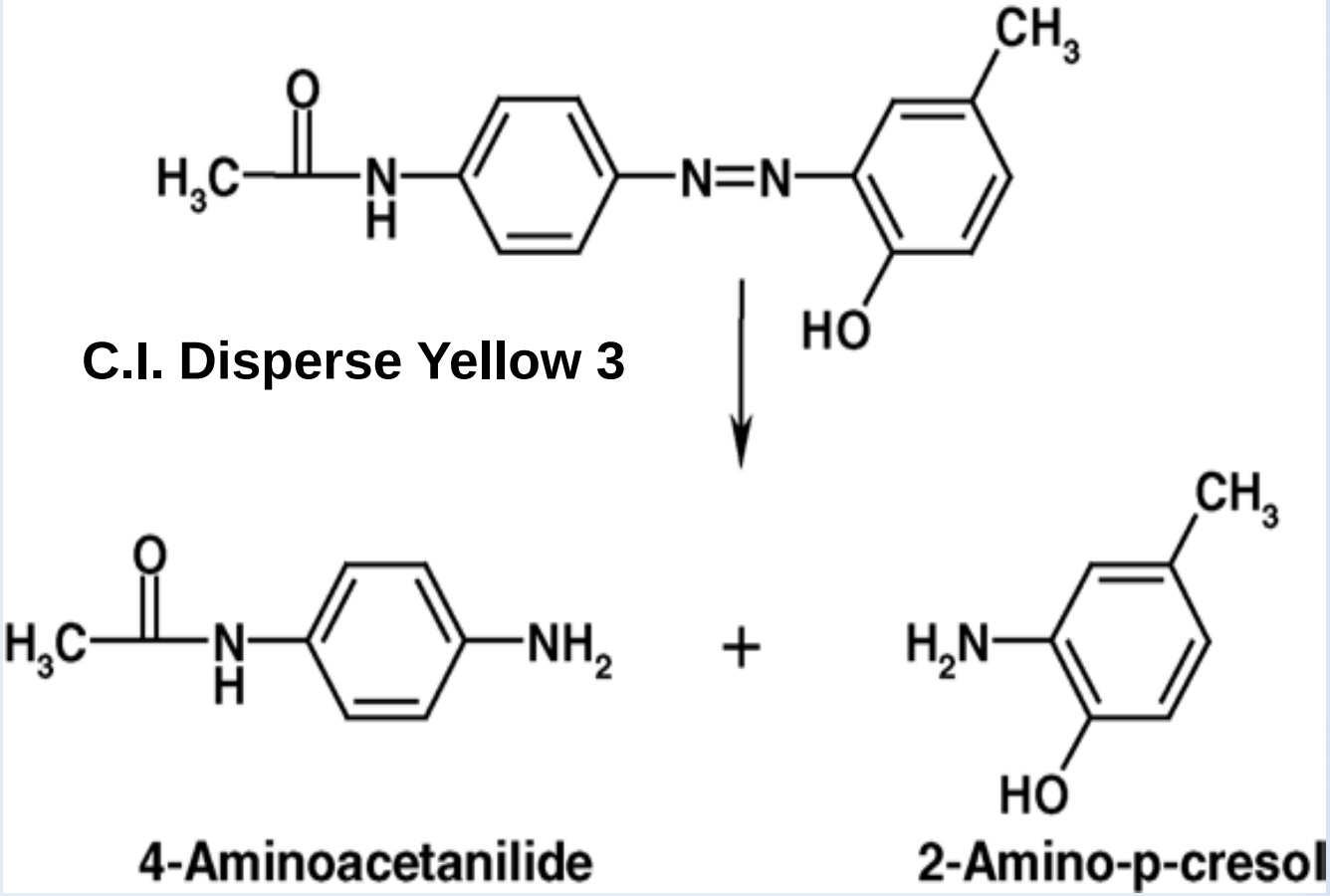
- **Absorption**
  - Dermal absorption is expected
  - Oral absorption is inferred
  - Inhalation unknown
- **Azoreduction**
  - Azo dyes undergo reductive cleavage of the azo bond and form aromatic amine metabolites
  - Metabolites: 4-Aminoacetanilide and 2-Amino-*p*-cresol

Proposed Mechanism Of Azo Reduction



Adapted from Levine (1991)

C.I. Disperse Yellow 3 and its Expected Metabolites

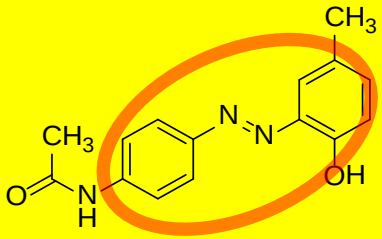


Genotoxicity of Metabolites

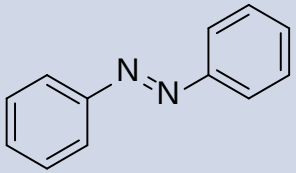
Chemical	Genotoxicity	
	In vitro	*In vivo*
4-Aminoacetanilide	*Salmonella* reverse mutation	Mouse bone marrow; chromosomal aberrations
2-Amino-*p*-cresol	*Salmonella* reverse mutation; mouse lymphoma forward mutation	Not tested

Structurally Related Chemicals

C.I. Disperse Yellow 3



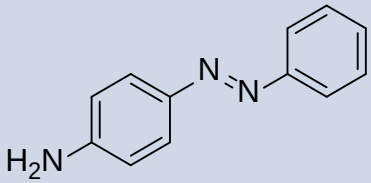
Azobenzene



Prop 65 listed

IARC 3

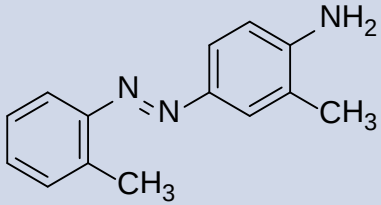
***p*-Aminoazobenzene**



Prop 65 listed

IARC 2B

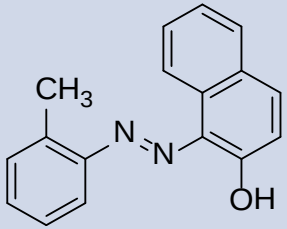
***o*-Aminoazotoluene**



Prop 65 listed

IARC 2B

Oil Orange SS

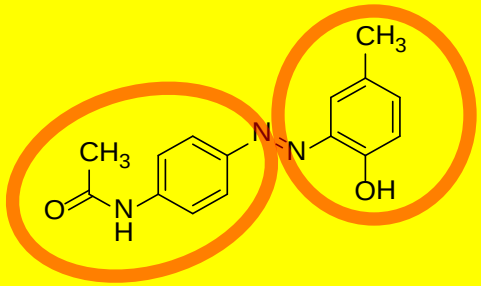


Prop 65 listed

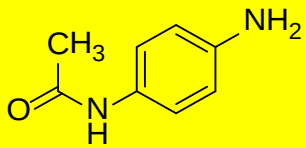
IARC 2B

Structurally Related Chemicals

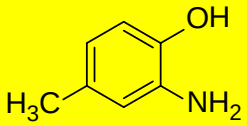
C.I. Disperse Yellow 3



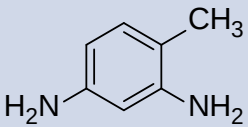
4-Aminoacetanilide



2-Amino-p-cresol



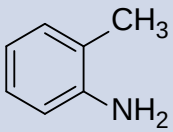
2,4-Diaminotoluene



Prop 65 listed

IARC 2B

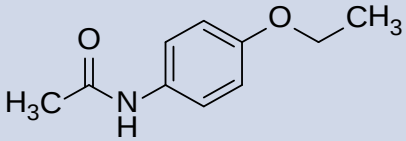
2-Aminotoluene



Prop 65 listed

IARC 1

Phenacetin



Prop 65 listed

IARC 2A

Carcinogenicity of Structurally Related Chemicals

Chemical	Liver		Other Sites	
	Mice	Rats	Mice	Rats
C.I. Disperse Yellow 3	F	M	F (hematopoietic system) M (lung)	M (Stomach)
Azobenzene	M			M (spleen)
p-Aminoazobenzene	M	M		M (skin)
o-Aminoazotoluene	MF	MF	MF (lung) F (soft tissues)	MF (lung)
Oil Orange SS			MF (bladder) M (intestinal)	
2,4-Diaminotoluene	F	MF		M (kidney, skin) F (mammary, lymphoma)
2-Aminotoluene	F		MF (blood vessels)	M (abdominal, scrotum, skin, spleen) F (mammary, bladder, spleen)
Phenacetin			M (urinary tract)	MF (urinary tract, nasal cavity)

Possible Mechanisms of Action

- Genotoxicity
  - Mutagenicity and clastogenicity by the parent compound and metabolites
  - Structural similarity with carcinogenic monoazo compounds and related aromatic amines that are genotoxic

Summary of Human Evidence

- Four case-control studies of bladder cancer risk among textile workers.
- Exposure-related limitations of all four studies:
  - C.I. Disperse Yellow 3 was just one of many disperse dyes used. C.I. DY3 was mentioned in only one study.
  - No exposure measures or cancer risk results for specific dyes.
- Two of the four reported significant associations for jobs with *potential* exposure to C.I. Disperse Yellow 3.
- The studies are inadequate to assess the relationship between C.I. Disperse Yellow 3 exposure and cancer risk.

Summary Of Animal Evidence

F344 rats

- **Males:**

- ↑ Benign and combined malignant / benign liver tumors
-Rare stomach tumors

- **Females:**

-No treatment-related tumors

B6C3F1 mice

- **Males:**

- ↑ Benign and combined malignant/benign lung tumors

- **Females:**

- ↑ Hematopoietic system tumors

- ↑ Benign and combined malignant / benign liver tumors

Summary Of Other Relevant Evidence

- *In vitro* genotoxicity in a variety of systems
- Metabolism to genotoxic metabolites
- Structurally similar to other carcinogens