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Azo Dyes: Structure–Carcinogenicity Relationships

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SUMMARY

Some structure–carcinogenicity trends are presented for that most important class of dye, the azo dye. For dyes that are carcinogenic and are resistant to chemical attack, such as true azo dyes, the dye itself is likely to be the pro-carcinogen. In contrast, azo dyes which exist in the hydrazone form are more likely to be broken down, e.g. reduced. In this case the pro-carcinogen is likely to be an amine breakdown-product of the dye and the ultimate carcinogenic potential can then be deduced from the availability of a suitable active site on the metabolite. Azo pigments, because of their extreme insolubility, are unlikely to be broken down, even if they exist in the hydrazone form.

INTRODUCTION

A recent paper[1] lists the animal carcinogenicity data of 97 dyes. However, no structure–carcinogenicity relationships were propounded. A survey of the data on the azo dyes makes several trends apparent. Since these are by far the most important class of dyes (more than 50% of commercial dyes are azo dyes),[2] it is important that such structure–carcinogenicity trends be reported.

RESULTS

The test results in the original paper[1] are ranked from A to E, A denoting a very thorough study and thus extremely reliable results, and E denoting

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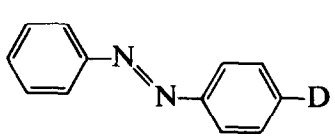
a cursory study with results that may be highly suspect. On the advice of our toxicology experts the E-class results are excluded from this analysis. D-class results should also be treated with caution as, to a lesser extent, should C-class results. A- and B-class results should be reliable.

The numbering of the dyes in this paper is the same as that used in the original paper to allow direct comparisons to be made.

DISCUSSION

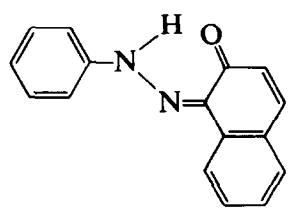
Information currently available on the metabolic activation of carcinogenic azo dyes indicates that the pro-carcinogen can be either the intact dye molecule or an aromatic amine metabolite. Dyes which are in general resistant to attack by various chemicals, for example reducing agents, are more likely to remain as discrete molecules and in this case the dye itself is likely to be the carcinogen. In the case of dyes which are more susceptible to chemical attack, the carcinogen is likely to be a breakdown-product.

Azo dyes may exist either as true azo dyes (i.e. in the azo form) or as hydrazone dyes (i.e. in the hydrazone form).[3] All aminoazo dyes and most azophenol dyes exist in the azo form. In contrast, most azonaphthol dyes exist either predominantly or exclusively in the hydrazone form.[3] Dyes in the azo form are in general more resistant to attack than dyes in the hydrazone form and this forms a useful initial classification:[4] azo dyes (more likely to remain as discrete molecules) and hydrazone dyes (more likely to be broken down, e.g. reduced).



$D = OH, NR_2$

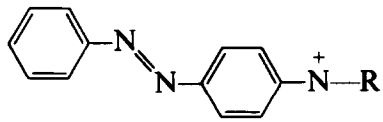
Azo



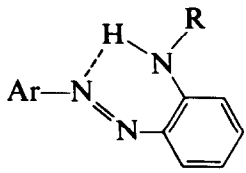
Hydrazone

Azo dyes

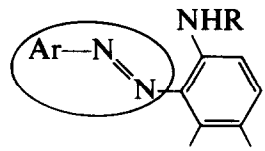
4-Aminoazobenzene disperse dyes such as Butter Yellow, **2** (Group I) are representative examples where the dye itself is the carcinogen. In these dyes, the ultimate carcinogen is thought to be the nitrenium ion (**1**).[5-8]



1

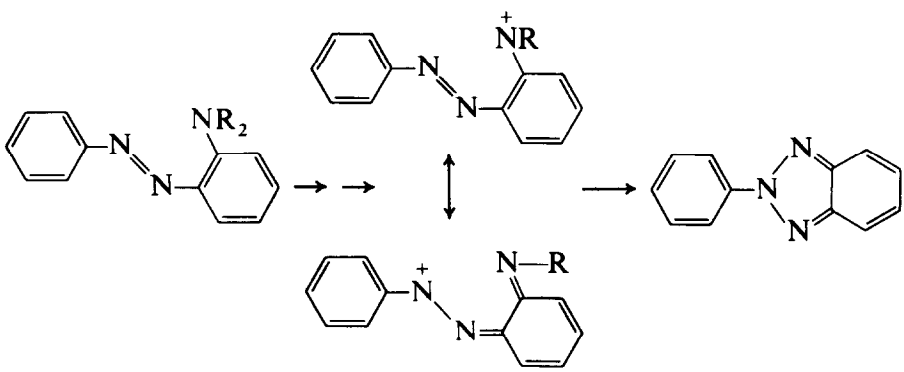


Hydrogen-bonding



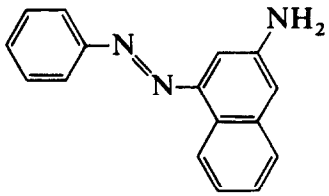
Steric hindrance of NHR group

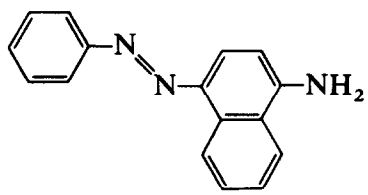
Indeed, the aminoazo disperse dyes cited in the earlier review (i.e. dyes devoid of water-solubilising groups such as sulphonic acid) may be divided into two groups: 4-aminoazo disperse dyes and 2-aminoazo disperse dyes. The former are all animal carcinogens (ranked A+ and B+): these are shown as Group I. In contrast, the 2-aminoazo disperse dyes are not animal carcinogens (ranked A− and C−): these are shown as Group II. This rather surprising but potentially useful observation could be due to several factors such as intramolecular hydrogen-bonding, steric hindrance or the facile oxidation to benzotriazole. Indeed, a plausible mechanism for the reported non-carcinogenicity of 2-aminoarylazo dyes is depicted in Scheme 1. Thus, the nitrenium ion from the 2-aminoarylazo dye is ideally set up for benzotriazole formation.



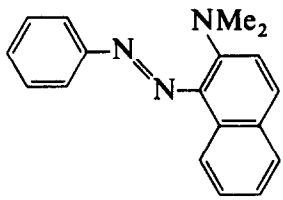
Scheme 1

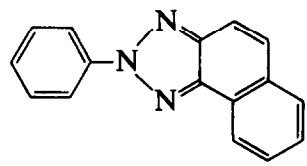
It would be interesting to test the model compounds shown below to help elucidate the reasons for the negative response of 2-aminoazo dyes.

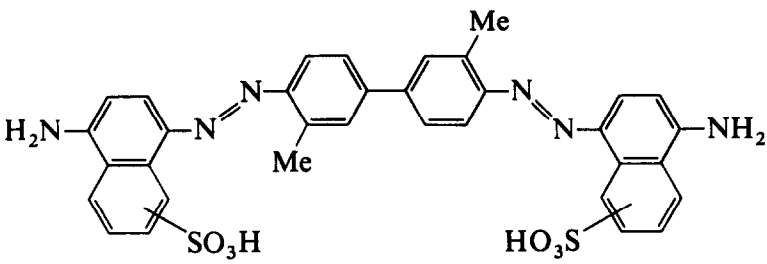




i.e. meta and *para* isomers of **6**







i.e. para isomer of **49**

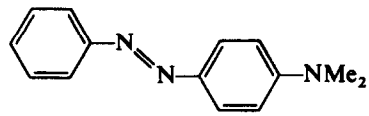
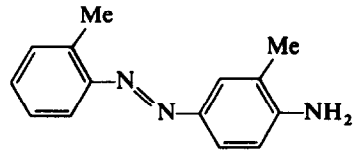
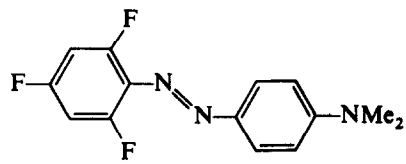
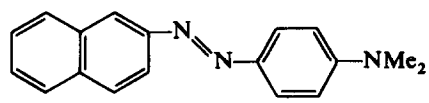
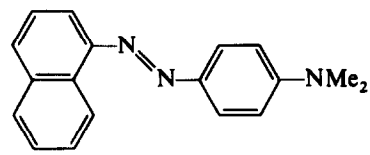
As mentioned earlier, azophenol dyes exist predominantly in the azo form. Just one dye of this type has been studied, namely **12** (Group III). This sulphonated azo dye gave a negative response, which may be explained by (a) the lack of an active centre for metabolic activation on the intact dye and (b) the high water-solubility encouraging excretion of the dye and thus restricting partition to the cell nucleus.

Hydrazone dyes

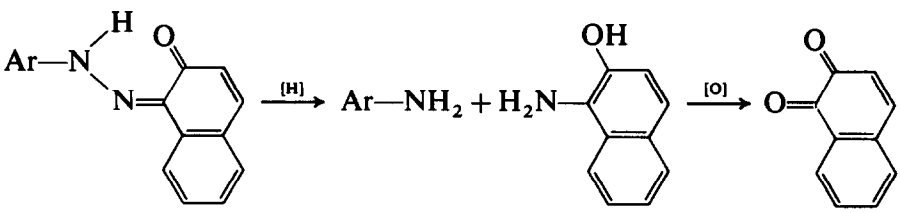
Hydrazone dyes are more likely to be reduced than azo dyes and therefore the carcinogenic potential of the breakdown-products needs to be considered. Reduction of a hydrazone dye generates an aromatic amine and an aminonaphthol[9] (eqn 1): the latter are known to undergo a facile oxidation to a naphthoquinone.[10]

Making the reasonable assumption that the generally sulphonated naphthoquinones (or aminonaphthols) are not carcinogenic, then it is the aromatic amine (Ar—NH_2) which determines the genotoxicity of the dye. Group IV lists the hydrazone dyes; all the dyes in this group are reported

GROUP I
Azo Dyes: 4-Aminoazo Disperse Dyes (All + ve)

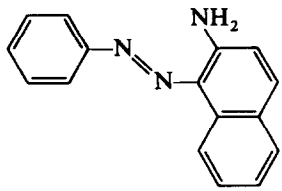
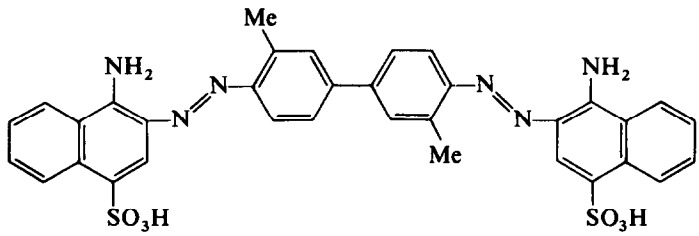
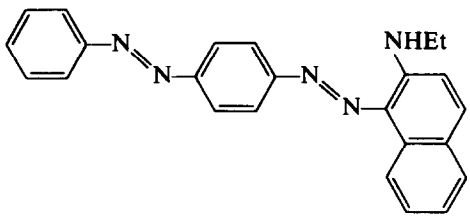
Compound	*Formula*	*Class*
2		B+
4		A+
29		B+
38		A+
39		B+

as animal carcinogens (ranked B+ and C+). In addition, the aromatic amines that would be liberated upon reduction are either known animal carcinogens or are expected to be carcinogenic. Two hydrazone dyes from this group, **50** and **51**, based on 3,3′-dimethylbenzidine, are both ranked B+ whereas a corresponding dye, **49** (Group II), which exists in the azo form and which is derived from the same benzidine diazo component, is

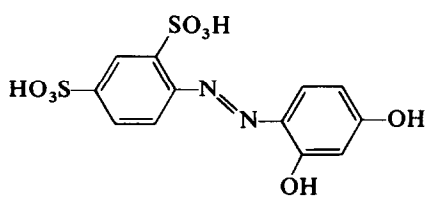


(1)

GROUP II
Azo Dyes: 2-Aminoazo Dyes (All – ve)

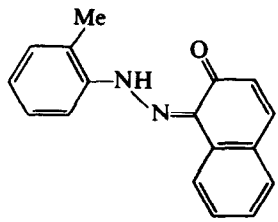
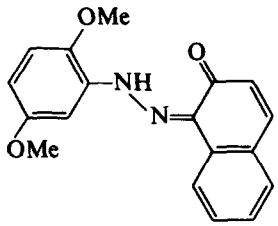
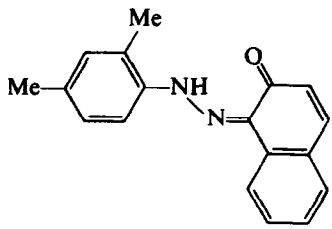
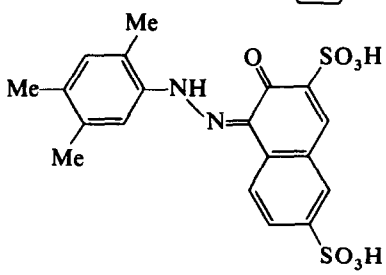
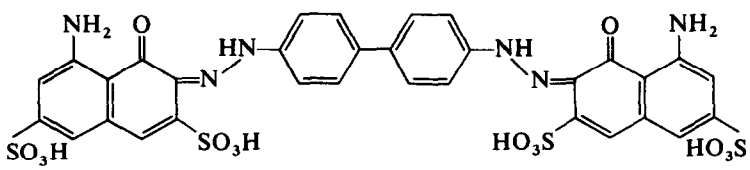
Compound	*Formula*	*Class*
6		A–
49		C–
55		C–

GROUP III
Azo Dyes: Azophenol (–ve)

Compound	*Formula*	*Class*
12		D–

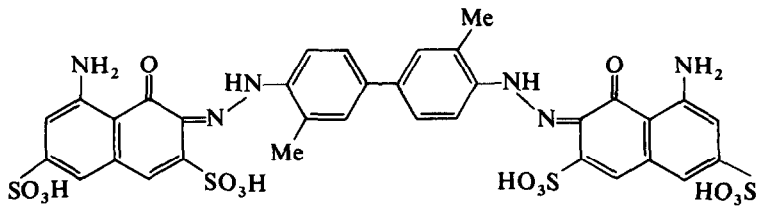
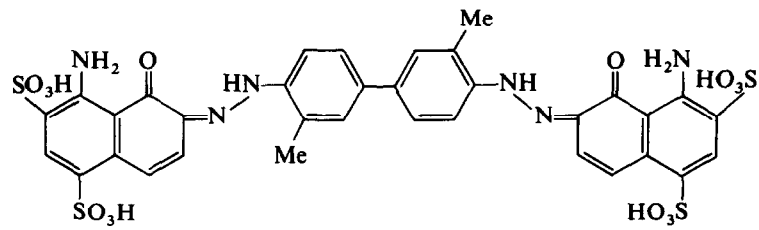
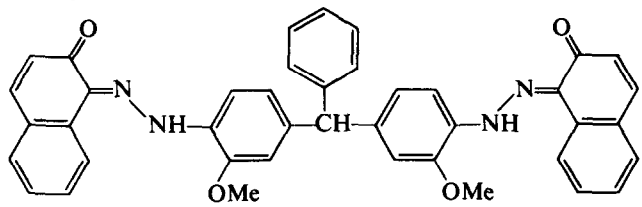
GROUP IV

Hydrazone Dyes: Generating a Genotoxic Amine Upon Reduction (All + ve)

Compound	*Formula*	*Class*
9		C+
11		C+
20		B+
21		B+
48		B+

(*continued*)

GROUP IV—*contd.*

Compound	*Formula*	*Class*
50		B+ cf. **49**
51		B+ cf. **49**
73		C+

ranked C−. This suggests that the azo dye is not being reduced to 3,3′-dimethylbenzidine, in accord with the proposed hypothesis.

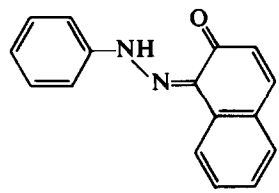
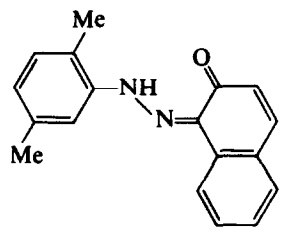
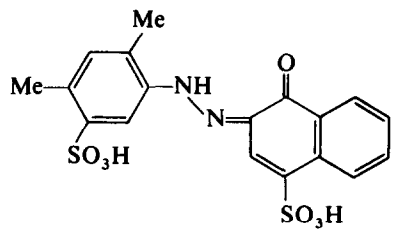
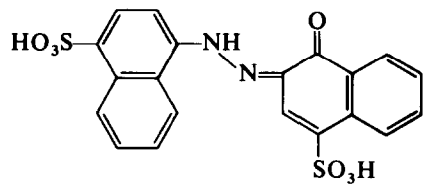
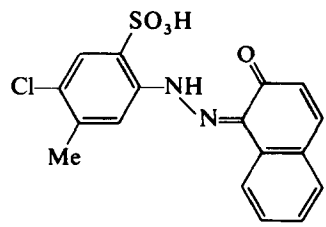
Group V lists the hydrazone dyes which are reported as being non-carcinogenic. Except for three dyes, the results fit the hypothesis since the liberated aromatic amines are all sulphonated and are therefore probably non-genotoxic. The three exceptions are **8**, which would liberate aniline, a weak animal carcinogen; **10**, which would liberate *para*-xylidine; and **53**, which would liberate the aminoazo dye **4** (Group I) ranked A+! It is the author's opinion that these three dyes could be animal carcinogens and it may be significant that the studies on these were of poor quality, ranked as D− (for **53**) and C− (for **8** and **10**).

Pigments

Group VI contains three pigments based on benzidine derivatives which exist as the hydrazone form but which are all ranked as A−. Pigments, by

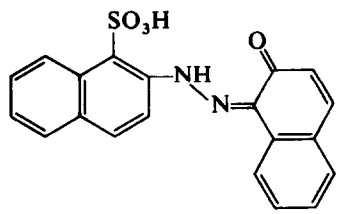
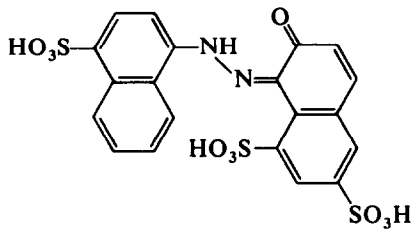
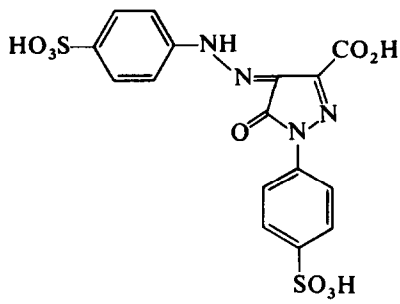
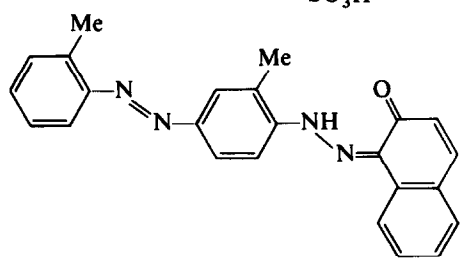
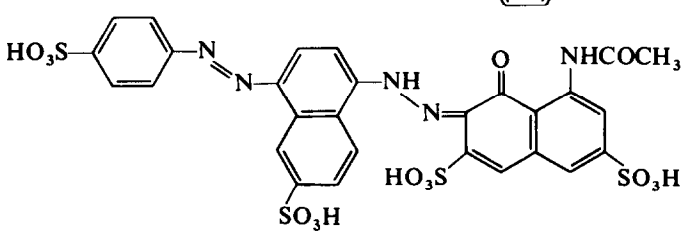
GROUP V

Hydrazone Dyes: Generating Non-genotoxic Amines (Sulphonated) Upon Reduction (Mainly – ve)

Compound	*Formula*	*Class*
8		C – (?)
10		C – (??) cf. **21**
14		A –
15		B –
16		B –

(*continued*)

GROUP V—*contd.*

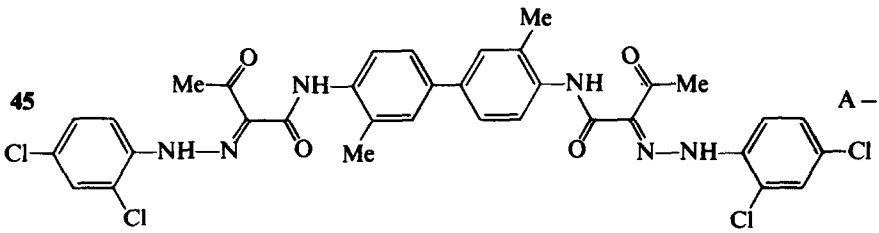
Compound	*Formula*	*Class*
17		B–
24		B–
26		B–
53		D–(??) cf. **4**
54		B–

GROUP VI

Pigments: Highly Insoluble Compounds (All −ve)

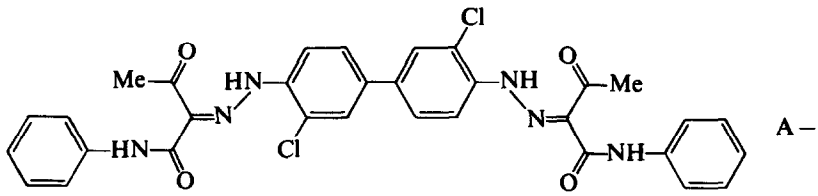
Compound	*Formula*	*Class*

45



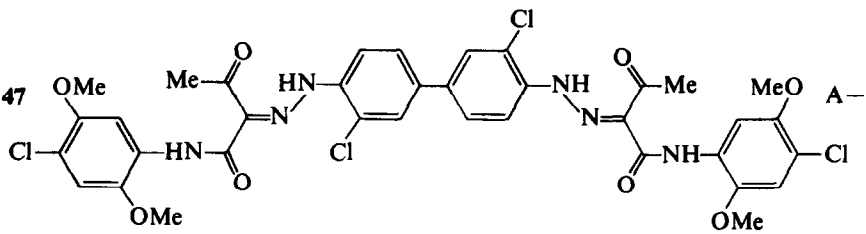
CI Pigment Yellow 16

46



CI Pigment Yellow 12

47



CI Pigment Yellow 83

definition, are extremely insoluble compounds and therefore will not be absorbed or reduced easily.[11] This could explain the observed negative response.

CONCLUSION

The above explanation is an attempt to introduce some rationale into the results presented in the original paper by Longstaff on the carcinogenicity of azo dyes. It is intended to provide some rough guidelines for use when evaluating which azo dyes are likely to be animal carcinogens, and to stimulate further discussion on this subject.

ACKNOWLEDGEMENT

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