BEITRAEGE ZUR GEOLOGIE DER SCHWEIZ - HYDROLOGIE	Bd. 28 I	S. 101 - 112	Bern, 1982

A REVIEW OF THE TOXICITY OF 12 FLUORESCENT DYES USED FOR WATER TRACING

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Abstract: A literature search for published toxicity information on fluorescent dyes used for water tracing yielded useful information on 12 substances: the fluorescent whitening agents CI28 and CI351, the dye intermediate amino G acid, the green fluorescent dyes Diphenyl Brilliant Flavine 7GFF, Pyranine, Lissamine Yellow FF and Fluorescein, and the orange fluorescent dyes Eosine, Rhodamine WT, Rhodamine B, Sulphorhodamine B and Sulphorhodamine G. Tests on mammals indicate a low level of both acute and chronic toxicity for all the tracers, but Rhodamine B, the only cationic dye, showed the highest toxic effects. Studies of carcinogenicity and mutagenicity often yielded conflicting results: the optical brighteners, Fluorescein and Eosin, were however judged nonmutagenic, while the Rhodamine dyes were suspect. Further screening of tracer dyes for mutagenicity is urgently needed. In aquatic organisms even prolonged exposure did not cause lethality until concentrations well in excess of those commonly persisting in tracer studies. However much lower concentrations were found to affect the development of eggs and larvae of shellfish. Persistent concentrations in tracer studies should therefore be below 100 µg/l.

Introduction

A large number of fluorescent substances have now been used as water tracers, but limited information is available on their toxicity in both aquatic organisms and mammals. Given an increasing concern on the effects of chemicals introduced into natural waters, there is a growing need for this information. A review of the available published studies has therefore been undertaken for the 12 fluorescent dyes listed in Table 1, whose exact structural formula is known. The fluorescent whitening agent CI15 is not included because this information is not available.

Table 1: Colour Index (3rd ed.) designations, dye type and bibliographical code used for the fluorescent dye tracers

Name	CI Number	Dye Type	Code
CI Fluorescent Brightener	28	Stilbene derivative	CI28
CI Fluorescent Brightener	351	Sulphostyryl derivative	CI351
Amino G Acid	-	Dye intermediate	AGA
Diphenyl Brilliant Flavine 7GFF	DY 96	Stilbene derivative	DY96
Pyranine	CI 59040	Pyrene	P
Lissamine Yellow FF	CI 56205	Aminoketone	LYFF
Fluorescein Sodium	CI 45350	Xanthene	FL
Eosine Sodium	CI 45380	Xanthene	E
Rhodamine WT	-	Xanthene	RWT
Rhodamine B	CI 45170	Xanthene	RB
Sulphorhodamine B	CI 45100	Xanthene	SRB
Sulphorhodamine G	CI 45220	Xanthene	SRG

Many dye manufacturers now produce a standard data sheet detailing handling and hazard information for their products, and this is a most useful primary source of information. It has also the advantage of referring directly to the material as supplied. However, because several manufacturers may produce chemically identical dyes, data is also available from collective tests, often conducted by manufacturers organisations. The wide-ranging tests sponsored by the American Dye Manufacturers Association and published in Dyes and the Environment are an example of such a source. Much published information results from environmental

concern, and this data is often most useful for our purposes, but medical studies, for instance of fluorescein in angiography, and experimental toxicology work on mechanisms of metabolism and excretion, are also useful. Finally, state regulatory agencies may be responsible for the instigation of toxicity tests and often provide useful reviews of toxicity data. The Toxic Substances List of the United States Department of Health, Education and Welfare, is an example of such a review dealing with data pertaining to toxicity in man.

There are two exposure patterns in toxicity studies; acute, referring to a single often large dose, and chronic, referring to prolonged ingestion through time. In acute studies lethality or pathological change are the main criteria of toxicity in the test subject. The former is a rather crude but readily identified measure, while the latter is often more sensitive but requires sacrifice of the test animals and expert investigation. More sophisticated criteria involve the measurement of biochemical changes in, for instance, enzymes. These methods are often very sensitive but may require an understanding of the mode of toxic action which is frequently not available. Finally, behavioural changes, such as avoidance reactions in fish, whilst integrating all biochemical and physiological changes, are frequently difficult to measure. In addition to these criteria the lack of impairment in reproduction, which often involves the most sensitive stage in an organism, is important. Finally, some compounds produce changes following prolonged exposure at low concentrations which are very different from the simple acute effects and involve the development of tumours in mammals or mutagenicity in lower organisms. Wide ranging studies have shown that mutagenicity and carcinogenicity of chemicals are generally correlated, and the former is now frequently used as a simple screening procedure for the latter, being much cheaper and more easily tested. However, there is not complete correspondence between the two, nor is the mutagenic response of different measurement systems and organisms consistant.

Before examining the data it is important to remember that dif-

ferences in test protocols and methods, in test species, route of administration and dose, all make comparison of toxicity data from different studies difficult. Furthermore, the standard of toxicity tests has improved with time, and some of the earlier studies may follow protocols no longer acceptable in modern toxicology. A more difficult problem is that the toxicity of dyes may well vary with the supplier or even batch of dye tested. For instance, some supplies of Rhodamine B contain a mutagenic impurity, but the dye itself is not mutagenic in the Ames test (Douglas et al., 1967). In addition to variation in impurities and other additives there are frequently differences in the supplied concentration of the dye-stuff which make comparison of different products difficult. No attempt has been made in this review to deal with these problems, but referal back to the original source will often clarify these points. Again the advantage of using a product from a single manufacturer, for which a hazard data sheet is available, are readily apparent. Finally when using dyes in the environment it must be remembered that photochemical and biological degradation of the tracer will occur, and the decomposition products may actually be more toxic than the parent compounds. A similar problem also arises at potable water intakes where chlorination of the water may cause chlorophenols to be formed from the original dyestuff. These often have a very astringent taste even at low concentrations and may again be more toxic than the original tracer. No studies of either of these problems have as yet been conducted.

The toxicity data reviewed have been collected in Tables 2 (mammal data), 3 (mutagenicity/carcinogenicity) and 4 (aquatic organisms). Toxicity criteria and measures have been selected to permit wide comparisons of all the dyes, and emphasis has been placed on comparative figures from a single source where possible. Where several sources are available they have been checked for conformity and the most toxic result recorded. The greater than sign (>) indicates that negative results were obtained at the highest test concentration or dose which was used, the true toxic effect occuring above this value. The reference source quoted is given on the table and quoted in full in the bibliography, including a code for

Table 2: Toxicity of fluorescent tracer dyes in mammals

Test	Animal	CI28	CI351	AGA	DY96	P	LYFF	FL	E	RWT	RB	SRB	SRG	Source
Acute Oral LD50	Rat	14.5	5.58	-	>15.0	>15.0	8.56	6.72	>1.0	>25.0	>0.5	>10.0	>10.0	2,5,8,9,11, 15,16,23,28, 56,62.
g/kg	Mouse	>10.0	>5.0	-	-	-	-	4.74	-	-	-	-	-	8,28.
Acute Intravenous LD50 mg/kg	Mouse	-	-	-	-	1050	110	300	550	430	a	b	b	26,36,40.
No Effect Acute Intraperitoneal mg/kg	Mouse	375	-	-	-	>50	>50	>91	>50	>167	5	>75	>75	1,12,31,37.
	Rat	400	-	-	-	-	-	500	250	-	125	-	-	3,8,16,23,31.
No Effect Chronic Oral. Dose (%) / Time (Weeks)	Rat	>1.0 / 106	>0.5 / 12.9	-	-	-	-	-	>2.0 / 18	-	0.1 / 18	-	-	2,6,8,21,28, 38.
	Dog	-	>1.0 / 12.9	-	-	-	-	-	-	-	-	-	-	28.
	Hampster	-	-	-	-	-	-	<0.75 / 8.6	-	-	-	-	-	10.
No Effect on Reproduction or Teratogenicity Dose/Time	Chronic	1% / 18m	0.1% / 3 gen	-	-	-	-	-	-	-	-	-	-	2,8,28,38.
	Acute	-	-	-	-	-	-	0.5g/kg	-	-	-	-	-	53.
Irritation c	Eyes	m	e	-	o	s	s	-	-	se	-	s	s	1,2,5,8,9,15,
	Skin	o	s	-	o	o	o	-	-	m	-	o	o	20,23,56.
Photoactivity d		o	v	-	-	-	-	+	+	-	v	-	-	1,17,18,23,30, 42,43,57.

Notes: a. LD50 Less than RWT. b. LD50 Greater than RB. c. o=none, s=slight, m=moderate, se=severe, e=extreme.
d. + = toxicity increased with light exposure. o = no effect. v = toxicity decreased with light exposure.

Table 3: Carcinogenicity/Mutagenicity data for the fluorescent tracer dyes

Test	CI28	CI351	AGA	DY96	P	LYFF	FL	E	RWT	RB	SRB	SRG	Source
Rec-assay[a] - Bacillus subtlis	-	-	-	-	-	-	0	0	-	-	-	-	58
- Escherichia coli	-	-	-	-	-	-	0	0	-	0	-	-	27
Disc test[a] - Escherichia coli	-	-	-	-	-	-	0	?	-	?	-	-	35
Petite mutations and gene conversions - Yeasts[a]	-	0	-	-	-	-	0	-	-	-	-	-	29,30,45.
Ames test[a,b,c] - Salmonella typhum	-	0/1	-	-	-	-	0/3	0/2	A+/1	0/5[d]	-	-	14,19,30,41,46, 47,48,49,55.
Chromosome aberrations in Chinese Hampster cells	-	0	-	-	-	-	-	-	?	+	-	-	13,14,33.
DCB Test for DNA alteration	-	-	-	-	-	-	A?	-	-	-	-	-	32
Dominant Lethal Mutagenicity Test Rat & Mouse-No effect g/kg	1.0	1.5	-	-	-	-	-	-	-	-	-	-	2,8,28,34,44.
Carcinogenicity - Rat & Mouse	0/3	0/3	-	-	-	-	0/1	0/3	-	0/3	-	-	6,8,18,22,24,
	-	-	-	-	-	-	?/1	?/1	-	+/2	-	-	25,38,59,60.

Notes: a O = nonmutagenic/carcinogenic, ? = possibly mutagenic/carcinogenic, + = mutagenic/carcinogenic,
b A = activation required.
c O/n, n = number of test results.
d Mutagenic impurities present in some commercial products.

the dyes reported (Table 1). The tables are for general information only, and a full evaluation of the original sources should be conducted by those using them. In order to update this review I would appreciate receiving details of additional sources of information as they become available.

Discussion

i) Toxicity in Mammals (Table 2)

Of the acute lethal data reported, the LD50 value (dose causing mortality of 50 % of the test animals) for oral administration is the best general indication of dye toxicity. The values are very high for all 12 dyes, although the maximum reported experimental doses for FL, E and RB are lower than desirable. In general none of the other dyes would be considered toxic by this criterion, the corresponding value for common salt being 8 to 10 g/kg. The acute intravenous and intraperitoneal administrations provide a test of the worst possible situation where there is effectively no barrier to movement of toxicant from the gut into the body. Only Rhodamine B and Pyranine are strongly absorbed from the gut but the fluorescent whitening agents appear to be particularly resistant to uptake. In general there is again no indication of substantial toxicity, and Lutty (1978) concluded that P, LYFF, E, RWT, and by extension FL, are suitable for angiography in the human eye. Given the higher intravenous and intraperitoneal toxicity of Rhodamine B and its strong absorption it is not surprising that in long term feeding studies, it was substantially more toxic than the other dyes tested, despite the fact it is metabolised to a less toxic compound in the body. Only LYFF of the other dyes is metabolised, although both FL and E combine with glucuronic acid and are excreted in the bile. Both FL and E have been shown to be more toxic when administration is combined with exposure to light, although more complete studies of the fluorescent whitening agents do not show this effect. In the case of E, release of bromine atoms after photo-decomposition is the probable mechanism for this effect. In general, personnel handling dyes should use protective gloves and clothing

and wash exposed skin and particularly eyes after any spillage. Excessive inhalation of dust from dye powders should also be avoided. No toxic effects are, however, expected either from handling dye concentrates or ingestion of dye at the concentrations used in tracer tests.

ii) Mutagenicity/Carcinogenicity (Table 3)

Toxicologists now generally agree that a hierarchial approach to the identification of potential carcinogens should be adopted. Initially a rapid screening of many chemicals can be carried out using micro-organism tests such as the Ames test. These should include several test strains and some form of metabolic activation. The results of such tests should be supported by parallel tests in other test systems such as yeasts or preferably more complex procedures to examine chromosome aberrations and DNA directly in vitro in mammal cells. Finally proven mutagens should be subjected to in vivo testing using long term feeding studies of mice and rats. These tests are the only definite way to prove a compound carcinogenic, but for the dyes examined, such studies are often found lacking with the respect to exposure period, numbers of surviving animals and adequate control (IARC 1977 and 1978). For this reason FL, RB and RWT are currently being retested using modern test procedures. The data in Table 3 are arranged according to the hierarchial scheme discussed above.

The fluorescent whitening agents tested show negative results in both micro-organism and mammal tests including in vivo feeding studies and the Dominant Lethal Mutagenicity tests, which measures the number of lethal mutations in off-spring caused by administration of the test compound to male rats. Rhodamine WT was positive in the Ames test with metabolic activation, a result confirmed by weak mutagenic activity in the chromosomes of Chinese hampster ovary cells. However, feeding studies at present underway will probably be negative (Douglas pers.comm.) Rhodamine B, while non-mutagenic, is Salmonella typhum proved positive in chromosome aberration and the Disc tests. Of 5 feeding studies, two were reported as positive but IARC (1978) report it's carcinogenicity as uncertain.

Preliminary Ames test on SRB are also positive, and it appears that the Rhodamine group as a whole is suspect. Fluorescein shows two possible positive results but overall appears to be non-mutagenic and non-carcinogenic. Similarly Eosin gave a positive result only in the Disc test and a possible *in vivo*, and therefore appears to be clear. Data are urgently needed for AGA, P, LYFF, SRB and SRG.

iii) Aquatic Organisms (Table 4)

Table 4: Toxicity of fluoresecent tracer dyes in aquatic organisms.

		CI28	CI351	AGA	DY96	P	LYFF	FL	E	RWT	RB	SRB	SRG	Source
LC50 mg/l -	96hr.Salmo gairdneri	-	130	>1000	-	-	>1000	1372	>100	>320	155	-	-	4,28,39,54.
	48hr.Salmo gairdneri	-	-	>1000	>1000	-	>1000	3420	>100	>320	506	450	-	9,39,54,57.
	96hr.Lepomis macrochirus	>1000	241	-	-	-	-	3433	-	-	379	-	-	8,39.
	96hr.Ictalurus punctatus	-	126	-	-	-	-	2267	-	-	526	-	-	28,39.
Maximum Lethal	48hr.Oryzias latipes	-	-	>3000	-	-	-	>3000	1500	-	-	-	-	57.
Concentration	48hr.Leuciscus idus	-	-	-	-	-	-	-	-	-	-	-	>500	5,23.
mg/l	96hr.Idua melanshes	-	-	-	-	>500	>500	-	-	-	-	-	-	5,23.
LC50 mg/l	96hr.Asellus aquaticus	-	-	>1000	-	-	>1000	-	-	>2000	550	-	-	54,61.
	24hr.Artemia salina	-	-	-	-	-	-	100-300	-	-	180	-	-	50.
No Effect	48hr.Crassostrea virginica	-	-	-	-	-	-	-	-	-	1.0	-	-	51.
Development of	48hr.Crassostrea gigas	-	-	-	-	-	-	-	-	10.0	-	-	-	52.
Eggs mg/l	48hr.Hemicentrotus pulcherrimus	-	-	-	-	-	-	10.0	-	-	10.0	-	-	50.
	48hr.Mytilus edulis		-	-	-	-	-	1.0	-	-	3.2	-	-	50.

RB and CI51 are the most toxic tracer dyes in fish, with the results for *Asellus aquaticus* confirming this for RB. However, for 48 hours exposure the maximum lethal concentration for RB is still 3 orders of magnitude higher than the visible threshold of this dye in water and over 5 orders greater than the minimum fluorometric detectability. Because the high concentrations present on dye injection are usually transitory, no restriction on dye concentrations should be necessary in the range 0 to 100 µg/l. Indeed, aesthetic considerations relating to the visible colouration of water by the tracer are more likely to limit tracer concentrations in populated areas. If prolonged continuous injection is planned, dilution of the dye stock solution will be effective in limiting concentrations adjacent to the input site.

The fish tests did not in any case produce a value for the threshold lethal concentration (the concentration at which no

additional mortalities result from continued exposure). The results for the development of the eggs and larvae of shellfish are therefore significant in indicating the toxicity to the most sensitive portion of the life cycle. RWT appears to be less toxic than RB, but in other organisms FL is equally or more toxic than RB. These tests suggest that in marine (and probably freshwater) systems dye concentrations should be maintained below 100 µg/l as far as possible. However, the most absorptive dye (RB) is readily cleaned from the flesh of shellfish on transfer to clean water, a finding also reported for several of the tracer dyes in fish. Further tests should be conducted using these sensitive systems to enable more comparative data on the dyes to be obtained.

Conclusions

In general, no hazard is anticipated in the normal conduct of tracer tests with fluorescent dyes. RB is generally the most toxic of the tracers investigated, is a proved mutagen/carcinogen and a poor quantitative tracer. It's use should therefore be discontinued. The other rhodamine dyes (RWT, SRB and SRG) are probably also mutagens and it may be necessary in situations where traced water passes into supply to use E as an orange fluorescent tracer. Photo-toxicity might then also need to be considered. FL and the fluorescent whitening agents are not hazardous but unfortunately can suffer from considerable photo-decomposition, limiting their use in quantitative tracer tests. More information is needed on the toxicity of AGA, DY96, P, LYFF, SRB and SRG.

Acknowledgements

I would like to thank all the dye manufacturers who made product data sheets and toxicity information available, including American Cyanamid Co.Ltd., Bayer UK ltd., Ciba-Geigy UK Ltd., Du Pont de Nemours and Co.Ltd., Hickson and Welch Ltd., Hoechst UK Ltd., and L.B.Holliday and Co.Ltd. The following individuals also provided information: Dr. R.Anliker and Dr. E.A.Clarke (Ecological and Toxicological Association of the Dyestuffs Manufacturing Industry), Dr. G.R.Douglas and Dr. E.R.Nestman (Health and Welfare, Canada), Dr. R.W.Hill (Imperial Chemical Industries Ltd.), Dr. B. Kilbey (University of Edinburgh), Dr. S.Leeny (National Cancer Institute), Dr. G.A.Lutty (John's Hopkins Hospital) and Dr. G.

Turner (Turner Designs Ltd.) Dr. J.F.Quinlan (National Park Service) provided data sources for the fluorescent whitening agents, and Dr. T.C.Atkinson (University of E.Anglia) made test data on Rhodamine WT available. Finally the University of Bristol funded the considerable amount of interlibrary loan material required in the compilation of this review.

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