J. Pharm. Pharmacol. 1985, 37: 1–12

REVIEW

The fate of pharmaceutical chemicals in the aquatic environment

MERVYN L. RICHARDSON AND JUDITH M. BOWRON

Thames Water Authority, New River Head, Rosebery Avenue, London EC1R 4TP, UK

Increased demands for potable water, especially where supplies are drawn from lowland rivers has necessitated a greater degree of water re-use. As water undertakings have a duty to maintain the wholesome quality of potable water supplies, increasing concern is being expressed over the presence of organic micro-contaminants (contaminants found at μg litre^{-1} concentrations). This study outlines some of the problems encountered in assessing the risk from pharmaceutical chemicals which might enter the water cycle from domestic and industrial sources. Analytical chemistry was of value for only a few of the 200 compounds studied. However, much useful information was derived from the human metabolic routes of the drugs and is collated in Appendix I. Biodegradation studies and other ecotoxicity/environmental toxicology data may be required to a greater extent in the future. Particular consideration is given to vulnerable sections of the population.

During the Catchment Quality Control (CQC) studies undertaken by Thames Water Authority (TWA) (Fish & Torrance 1977, 1978; Wood & Richardson 1978, 1980; Nicolson et al 1981; Richardson & Bowron 1983; Bowron & Richardson 1984) it became apparent that pharmaceutical chemicals would enter the water cycle via two main routes.

(1) The industrial route: i.e. a point discharge to a sewage treatment works where the manufacturer or packer of a pharmaceutical product might incur 1–5% wastage of their product. This could find its way to drain and hence to the sewage treatment works, as a normal consented discharge. This percentage wastage of chemicals is low compared with many other industries because of the care necessary in handling very high cost chemicals often in controlled environments such as sterile packaging areas. Furthermore, the pharmaceutical industry works to stringent guidelines such as Good Manufacturing Practice and the Medicines Act.

(2) The 'domestic route': most pharmaceutical chemicals, both proprietary and ethical preparations, having left the factory, will be dispensed or sold to the public. These preparations will be administered either in the home, or in hospitals or clinics.

Excreta containing such drugs or their metabolites, or excess drugs if sluiced away, will reach sewage treatment works (STWs).

At STWs there are three principal possible fates for any individual pharmaceutical chemical:

(a) It might be ultimately biodegradable, i.e. to carbon dioxide, water, e.g. aspirin.
(b) It might undergo some form of metabolism or rather partial degradation e.g. penicillins.
(c) It might be persistent e.g. clofibrate.

Hence STWs effluent could contain either intact or partially degraded pharmaceutical chemicals.

STWs effluents discharge into rivers, many of which are subsequently abstracted for potable water supply purposes. As it was assumed that drug residues would survive the various water treatment processes, there seemed to be a distinct possibility that pharmaceutical chemicals at low concentrations (μg litre^{-1}) would be present in potable water supplies. Therefore, the question arises 'What is the long term public health risk of ingesting such drugs and/or their metabolites for up to about 70 years at a fraction (~1%) of their therapeutic dose?'

Treatment at STWs and waterworks could be improved by costly and advanced procedures such as activated carbon plants. These can be effective for the removal of a wide range of noxious organic chemicals, thereby improving the position relating to otherwise recalcitrant organic chemicals.

It was appreciated that drug prescriptions fall into two major categories:

(a) Short term—in this situation drugs are usually taken for a period of up to, say, two weeks and any excess usually retained in the household, returned to

the pharmacy, disposed of to refuse or flushed into the drain as earlier indicated.

(b) Long term—in this situation there is unlikely to be any excess drug to waste unless the formulation/prescription has to be changed.

It was also appreciated that whilst it is an acceptable risk to administer chemicals having high biological activity like cytotoxic drugs for instance, to the chronically ill, such a risk may not be acceptable for neonates and in pregnancy, despite the very low levels.

Furthermore, although many of the drugs studied in this investigation have been known and prescribed for many years, half a century in a few cases, this is insufficient reason for complacency.

In view of the foregoing the investigation was undertaken.

DETAILS OF THE INVESTIGATION

In the case of drug manufacturers and compounders within the TWA freshwater catchment, it was a reasonably easy matter to obtain, in strict confidence, an estimate of the quantities of each pharmaceutical chemical wasted to drain on a per annum basis (Fish & Torrance 1977, 1978; Wood & Richardson 1980). It was then simple to calculate the predicted concentration at the various downstream potable water abstraction points. On the assumption that the average person drank two litres of water per day an estimate of the likely ingested dose was made.

However, during our preliminary studies (Wood & Richardson 1980), it became apparent that wastage from manufacturing units was likely to contribute only marginally to the overall load of pharmaceutical chemicals that could be found in potable water supplies, at least as far as TWA catchments were concerned. The major source would be the home and hospitals, and for this reason a water authority would be unable to seek control, as would be the case with an industrial discharge.

Chemical analysis was then considered but it was rapidly concluded that this would not be practical except for a few pharmaceutical chemicals.

Firstly, the analysis of such chemicals in water, a surprisingly difficult matrix, at $\mu g\ litre^{-1}$ concentrations would be likely to involve considerable resources for a comparatively small number of chemical compounds. That is, a small number compared with 10 000+ industrial and related chemicals used in the EEC in quantities >1 tonne per annum, all of which are likely to enter water resources. Secondly, it was appreciated that human metabolism and sewage works treatment would be likely to modify the structure of the pharmaceutical chemical, in many cases removing the analytical determining group. Thirdly, all the pharmaceutical chemicals would be present in admixture with industrial, domestic and allied chemicals.

Whilst analysis was found to be practical for a few pharmaceutical chemicals, the separation techniques at the predicted concentrations were a major problem. This was so notwithstanding the unlimited size of the samples available, a very different situation from clinical analysis. In the latter, sample volumes are small, whereas volumes of samples for water analysis can be 20 litres before preconcentration.

Because of these analytical chemical problems it was decided to predict the quantities/concentrations of pharmaceutical chemicals that were likely to be present in the River Lee as a worst case situation.

A 'rule of thumb' calculation indicated that if one tonne of a pharmaceutical (or other chemical) was evenly discharged to the rivers in England and Wales over one year then a concentration of very approximately $0{\cdot}1\ \mu g\ litre^{-1}$ was likely to be achieved in the River Lee, assuming that no degradation or metabolism occurred.

The River Lee is a source of potable water for North London and during summer months and dry weather conditions it can be composed of some 60% of STWs effluent.

The concentration criterion of $0{\cdot}1\ \mu g\ litre^{-1}$ was selected for this study as in 1975 this concentration was one order of magnitude more stringent than any quoted in water quality criteria (Fish & Torrance 1977, 1978; Wood & Richardson 1978, 1980).

A computer print-out of drugs prescribed by general practitioners (200 or more prescriptions) for the year 1976 was obtained from the Department of Health and Social Security. This excluded drugs administered in hospitals and private practice. Similar details were obtained from the Proprietary Association of Great Britain for proprietaries.

The document gave the number of tablets, capsules, injectables etc. prescribed. These were then translated into tonnes of active pharmaceutical chemical ingredients. A total of 716 prescribable preparations were considered; this gave a list of 1600 chemicals. Some active ingredients were contained in over 30 formulations. Approximately 170 pharmaceutical chemicals were found to be used in excess of one tonne per annum or, using the factor referred to above, gave a predicted concentration of $0{\cdot}1\ \mu g\ litre^{-1}$ or above in the River Lee. Additional pharmaceutical chemicals were added to this list, see

Appendix I. e.g. drugs used in cancer chemotherapy because they are noxious.

The pharmaceutical chemicals were then individually considered with particular relevance to the information collated in Appendix I, e.g. metabolism, presence in maternal milk, ability to cross the placenta, plasma half life. This information was obtained from standard textbooks such as Martindale—The Extra Pharmacopoeia, British Pharmaceutical Codex, Association of the British Pharmaceutical Industry Data Sheet Compendium. The information was enhanced by on-line searching.

This exercise led to the following deductions:

(a) That a significant number of pharmaceutical chemicals undergo Phase I and II mammalian metabolism usually yielding conjugates. The toxicity and pharmacological activity of these is much lower than that of the parent compound. Microbial metabolism can also lead to similar transformations. Furthermore, such conjugates can be hydrolysed in STWs by enzymic processes, e.g. β-D-glucuronidase, to yield innocuous but stable products. Many of these will not have the analytical determining groups possessed by the parent compound.

(b) Whilst pharmaceutical chemicals are studied in depth for their pharmacological and clinical action, they are little studied for their environmental effects and ecotoxicity.

In view of this, the pharmaceutical chemicals listed in Table 1 were selected for biodegradation studies on the basis of the high quantity in use, potential for being noxious or because on reviewing the literature the drug seemed to survive sewage treatment. (Cytotoxic drugs were considered later.)

The methods for testing were those recommended by the Department of Environment, Standing Committee of Analysts (1981) and by King (1981).

Degradation or metabolism in the pharmacological sense is ultimately aimed at the removal of a biological effect; but biodegradation from the ecotoxicological stand point requires a different approach. It must be considered whether the compound is likely to be ultimately degraded, partially degraded (in which case metabolites may be of importance), or persistent. In the last instance further studies may be needed.

As earlier indicated, there was the need to consider chemical analysis.

This was undertaken in two ways:

(i) Gas chromatography–mass spectrometry (GC–MS). This technique is now used for indicating the presence of organic micro contaminants in various water samples. Suitable preconcentration (liquid–liquid extraction or by use of XAD resins) of samples is needed and in fact concentration factors of up to 10 000 can be achieved. From this type of analysis, lists of chemicals are identified in such samples. GC–MS has the disadvantage that, in general, it will only detect those chemicals which are volatile or easily derivatized to volatile chemicals, a maximum of some 20–25% of chemicals considered to be present in many water samples.

Table 1. Summary of biodegradability test results.

Compound	Result
Amitriptyline	Non-biodegradable
Ampicillin	48% biodegradable
Aspirin	Readily biodegradable
Caffeine	Readily biodegradable
Chlorhexidine	Non-biodegradable
Clofibrate	Non-biodegradable
Codeine phosphate	Non-biodegradable
Dextropropoxyphene	Non-biodegradable
Ephedrine	Readily biodegradable after acclimatisation
Erythromycin	Non-biodegradable
Ibuprofen	Inherently biodegradable
Menthol	Readily degradable
Meprobamate	Non-biodegradable
Methyldopa	Non-biodegradable
Metronidazole	Non-biodegradable
Naproxen	Non-biodegradable
Nicotinamide	Readily biodegradable
Paracetamol	Readily biodegradable after acclimatisation
Phenylpropanolamine	Readily biodegradable after acclimatisation
Sulphamethoxazole	Non-biodegradable
Sulphasalazine	Non-biodegradable
Tetracycline	Non-biodegradable
Theobromine	Readily biodegradable after acclimatisation
Theophylline	Readily biodegradable
Tolbutamide	Non-biodegradable

In fact very few pharmaceutical chemicals were identified by this technique (see Table 2).

In addition to samples of river and potable supply water, a sample of hospital effluent was examined and apart from methaqualone (see page 5) few pharmaceutical chemicals were identified. Disinfectants and detergents were most in evidence.

The EEC, within its COST 64b project, has made a computer-based compilation (CICLOPS) of those organic micro-pollutants reported worldwide. Few pharmaceutical chemicals are included. However, one of the more extensive studies is that by Watts et al (1983) of the Water Research Centre, Medmenham who report the presence of several antimicrobials (erythromycin, sulphamethoxazole, tetracycline) and theophylline, in river water samples. They used field desorption mass spectrometry and high performance liquid chromatography.

(ii) *Analysis of individual and groups of chemicals.* Whilst gas chromatography and high performance liquid chromatography have been used to identify specific pharmaceutical chemicals (Table 2), further compounds have been studied using immunoassay techniques. These have been in use for many years in clinical analytical chemistry but their application to water chemistry is new and shows considerable promise for the larger molecules. Aherne (1984) and Aherne & English (1984) have successfully used such techniques for the assay of methotrexate, progesterone, norethisterone and ethinyloestradiol in various river and potable water samples. After sample concentration by lyophilization, detection limits of between 5 and 10 ng litre^{-1} were achieved.

Table 2. Pharmaceutical chemicals found in sewage (S), sewage effluent (E), River (R) and potable waters (P). Samples by analysis.

Compound	Sample type	Concn (litre^{-1})	Remarks
Aspirin	(E)	~1 μg	See text*
Caffeine	(E)	~1 μg	See text*
	(P)	>1 μg	See text*
Clofibrate	(R)	~40 ng	
Diazepam	(E)	<1 μg	See Appendix 1* and
	(R)	~10 ng	Waggott (1981)
	(P)	~10 ng	
Dextro-propoxyphene	(R)	~1 μg	See text*
Erythromycin	(R)	~1 μg	See Watts et al† (1983)
Methaqualone	(S)	~1 μg	See text*
Methotrexate	(S)	~1 μg	See text and Aherne
	(R)	<6·25 ng	& English (1985)
	(P)	<6·25 ng	
Morphinan substructure	(R)	<1 μg	See text*
Oral contraceptives	(R)	<0·2 μg	See text and Aherne
	(S)	<0·1 μg	& English (1985)
Penicilloyl groups	(R)	⩾25 ng	See text
	(P)	⩾10 ng	
Sulphamethoxazole	(R)	~1 μg	See Watts et al (1983)†
Tetracycline	(R)	~1 μg	See Watts et al (1983)†
Theophylline	(R)	~1 μg	See Watts et al (1983)†

* GC analysis. † HPLC analysis.

MATTERS HIGHLIGHTED

The experimental findings from the biodegradation and analytical chemical studies, coupled with the information retrieved from the literature, suggested a significant conclusion. This was that very few pharmaceutical chemicals were likely to survive STWs treatment, river retention, reservoir detention and waterworks treatment in the form of the intact molecule. The conclusion enhances the view that advanced treatment, such as the use of activated carbon is unlikely to be required at least for pharmaceutical chemicals.

Of those pharmaceutical chemicals that were not ultimately degraded, most were likely to be metabolized to pharmacologically inactive sub-structures or conjugates. Even if these were likely to persist through various water treatment processes and be present in water supplies, the concentrations in the majority of instances would be unlikely to pose a public health risk. The same deduction would also apply to a large extent to the parent molecules. The predicted ingested quantities, as can be seen from Appendix I, are so small that a life-time ingestion of a pharmaceutical chemical from potable water would only give of the order of one day's recommended therapeutic dose. For example, 70 years' exposure to paracetamol would give four times the adult daily dose, to diazepam one day's dose, and to clofibrate one-sixth of a daily dose.

Antineoplastic agents and immunosupressants

Notwithstanding the above predictions, particular attention was given to drugs used in cancer chemotherapy, and immunosuppressive agents. This was because many of these are mutagens, mitotic inhibitors, antimetabolites or alkylating agents.

Methotrexate was chosen by Aherne & English (1985) as a model compound because it may be used in substantial doses (up to 22 g day^{-1}), its use is widespread, and a sensitive immunoassay was available for its measurement.

Apart from a sewer immediately downstream of a large oncology clinic, no methotrexate concentration in excess of 6·25 ng litre^{-1} (the limit of detection) was found in any sample of river or tap water examined by Aherne & English (1985). Therefore, it was considered reasonable to deduce that there should be no risk from such potentially noxious chemicals.

Morphinan substructure

Results from the chemical analysis (GC–MS) indicated the presence of a morphinan sub-structure in a sample of river water downstream from a STW receiving much hospital effluent. The matter was pursued with the Pharmaceutical Society of Great Britain and the Regional and Area Health Authority Pharmaceutical Officers. It was considered that the presence of this structure could be due to excess drugs such as codeine, morphine or related compounds being sluiced away instead of being incinerated which is the procedure preferred by the

Pharmaceutical Society Inspectorate for disposal of such unwanted drugs. Adoption of this procedure resulted in this substructure not being found in subsequent river water samples.

Methaqualone

In this respect it was interesting that methaqualone was found in a sample of hospital effluent. This was at the time when use of this drug was being discontinued and hence it was deduced that surplus drug was being sluiced away.

Oral contraceptives

In the past decade, concern has been expressed over the possible presence of oral contraceptives in water samples. Aherne & English (1985) reviewing this noted their apparent absence (norethisterone <10 ng litre^{-1} and ethinyloestradiol <5 ng litre^{-1}) in the samples of potable water they examined. They also indicate that had they been present at the quoted limit of detection 10 and 5 ng litre^{-1} respectively this would have equated to an individual ingesting 1/17 500 and 1/2000 of the prescribed daily dose.

Penicillin allergy

Potential concern has also been expressed over the possible allergenic effects from penicillins. These had been found to be partially biodegradable (to ~50%) in a conventional biodegradation study (Water Research Centre). It was postulated that a penicillenic acid may be formed which in turn might form the penicillolyl determinant. Attempts were therefore made to assay the latter by an immunoassay technique (Wal et al 1975). The results indicated that, if present, such determinants would be unlikely to exceed 25 ng litre^{-1} in river water and 10 ng litre^{-1} in potable water.

Considerable doubt has been expressed by Dewdney & Edwards (1983) over Siegel's (1959) extrapolated figure of 0·24 μg as a single dose. Even if this literature figure were accepted as being capable of causing a reaction in a sensitive person, Dewdney & Edwards' study of the literature failed to identify any reference that indicated an amount lower than 0·24 μg would cause a reaction. The immunoassay findings were at concentrations some 100 fold less than this and hence there should be no risk of a sensitization reaction from potable water supplies.

Aspirin and salicylates

As aspirin is ultimately biodegradable, it was surprising that it was found in a number of river water samples (Water Research Centre—see Table 1 and CICLOPS). Moreover it was considered that its presence was due to it being a microbial metabolite of naphthalene oils, resulting from oil spillages.

Caffeine

The caffeine present was considered to be more attributable to beverages than from its use as a drug.

Dextroproxyphene

1,1-Diphenyl-butene (1,1-Db) was found to be present by GC–MS in a sample of river water. 1,1-Db by structure activity relationships was considered to be ultimately degradable. A literature search indicated that 1,1-Db was a pyrolysis product of dextropropoxyphene, Millard et al (1980) suggesting that 1,1-Db was being formed in the injection port of the GC. Hence, the presence of dextropropoxyphene was indicated in the sample considered. This was supported by spiking a sample from another river.

VULNERABLE SECTORS OF THE POPULATION

Young infants/foetus

Many drugs can be secreted into mothers milk and/or cross the placenta, see Appendix 1. The risk to the very young or to the foetus is hence much greater from a mother being prescribed pharmaceutical preparations than the risk to a young infant of drinking water which may contain a few μg litre^{-1} of a drug. See Appendix 1.

Renal dialysis patients

These patients are likely to be in contact with up to 100 times the volume of water consumed per head by the population at large. Also the route of exposure by-passes the normal gastrointestinal processes. Thus it is important to consider the effects of micro-contaminants as obviously the patient's life span should not be reduced by the presence of such impurities in the water used. However, as the impurities would have to pass through a dialysis membrane to reach the patient, small molecules, such as the halomethanes are likely to pose a greater risk than pharmaceutical chemicals whose molecules are often large, especially if they are conjugated. It is stressed that naturally occurring residues of aluminium salts or aluminium salts used for flocculation in water treatment are likely to be of much greater concern than drug residues.

In making a risk assessment it must not be overlooked that a patient receiving a transplant kidney is likely to receive immunosuppressive drugs for a considerable period. In view of their mutagenic

properties, any additional risk from mutagens that might be present in water will be minimal.

Population groups with enzyme deficiencies

The predicted presence of most drugs as biologically inactive metabolites rather than the pharmacologically active parent compounds in re-used water is of significance when enzyme deficiencies are considered. Glucose-6-phosphate dehydrogenase deficiency, for example, occurs among the population, the percentage being higher in certain Mediterranean countries. This deficiency can lead to haemolytic anaemia following the ingestion of certain drugs, including primaquine, phenacetin and aspirin. There might be cause for concern over residues of such drugs in potable water if it were not for the low predicted concentrations and the lack of pharmacological activity of the residues.

The situation is similar for mono-oxygenases. Küpfer et al (1982) report on several examples of genetic polymorphism of drug oxidation in man (and rat). They indicated that between 1–9% of the population they studied were deficient in their relative ability to effect the oxidative metabolism of debrisoquine, sparteine and phenformin. In 1976, the predicted concentration of phenformin in the River Lee was 0·15 μg litre^{-1} with the other two drugs at less than 0·1 μg litre^{-1}. However, even if this deficiency occurred in a significant proportion the same mitigating factors apply as before. Normal persons will excrete the drugs as hydroxylated conjugates or mic· ·ial metabolism will occur during STWs' processes and the concentrations are low.

Drug–drug and drug–food interaction

Such interactions, whilst theoretically possible, are unlikely to be caused by drug residues in water. This is again mainly due to the lack of pharmacological activity of most relevant residues.

Inhibition of both microsomal and non-microsomal enzymes has been shown in man. The latter effect is exemplified by the monoamine oxidase inhibitors which increase sensitivity to some sympathomimetic amines found in certain foods and other drugs. The inhibition of tolbutamide metabolism by dicoumarol, phenylbutazone, phenyramidol and sulphaphenazole is a microsomal effect which can lead to the plasma elimination half-life of tolbutamide being increased fivefold.

The drugs causing enzyme inhibition are not thought likely to be present in re-used water at either sufficient concentration or retain sufficient properties of active form to cause any problems.

OTHER USES OF DRUGS

Whilst this review outlines the probable effects of pharmaceutical chemicals used for human therapy, no detailed consideration has been given to veterinary drugs.

There is little or no evidence to suggest that a different pattern should emerge for drugs used for treating farm animals, but the situation is not necessarily the same for substances used for treating fish. Such chemicals, in many cases, will be added either directly to water, or to fish food. Fish in many cases have different metabolic mechanisms. Furthermore, waste waters from fish farms will not be subject to STW processes.

Hence, further investigation is considered necessary for drugs such as nitrofurans and nitrothiazoles which can be used for disease control in fish farming.

In fact, the use of this type of antimicrobial in fish farms upstream of potable water abstraction points cannot be condoned. Care is also required where previously accepted veterinary products are used as industrial biocides.

CONCLUSIONS

Catchment Quality Control studies have indicated that pharmaceutical chemicals may enter potable water supplies from both domestic sources, including hospitals, and from manufacturing units. The latter is likely to be the lesser source of organic micropollutants and such discharges can be controlled.

Some 200 pharmaceutical chemicals were considered in the study described. It was appreciated that many would metabolise to innocuous substances e.g. conjugates. Such conjugates may then be hydrolysed to pharmacologically inactive compounds by STW processes.

Biodegradation studies made on 25 of the major use drugs indicated which drugs would survive STW processes and which were ultimately or partially degraded during such treatment. In considering the effects of new pharmaceutical chemicals, it is advocated that ecotoxicological/environmental toxicity tests such as biodegradation testing should be included in the portfolio of tests undertaken.

Attempts to analyse for individual pharmaceutical chemicals were not fruitful. However, such analyses as were possible indicated that the concentrations were <1 μg litre^{-1} in most cases. Some analyses of the more refractory compounds are recommended to be undertaken on an infrequent basis.

Acknowledgements

The authors thank Thames Water Authority for permission to publish this paper and to state that the views expressed are their own and not necessarily those of the Authority or the Pharmaceutical Society of Great Britain. They wish to express their appreciation of the assistance given by scientists in industry, trade and research organisations, Government Departments and from the Pharmaceutical Society's staff.

REFERENCES

Aherne, G. W. (1984) Proc. Anal. Dir. Royal Soc. Chem., May, 177–179

Aherene, G. W., English, J. (1985) Ecotoxicology and Environmental Safety, in the press

Bowron, J. M., Richardson, M. L. (1984) in: Pawlowski, L. Verdier, A. J., Lacy, W. J. (eds) Chemistry for Protection of the Environment, Toulouse, France, 9–25 Sept. 1983. Elsevier, Amsterdam pp 109–117

Department of the Environment (UK) – Standing Committee of Analysts (1981) Assessment of Biodegradability 1981, in Methods For the Examination of Waters and Associated Materials, HMSO

Dewdney, J. M., Edwards, R. G. (1983) in: Woodbine, M. (ed.) Antimicrobials and Agriculture to be published in 1984 by Butterworths. (Proc. Int. Symp. on Antibiotics and Agriculture – Benefits and Malfits, Univ. Nottingham, March 1983.)

Fish, H., Torrance, S. (1977) J. Nat. Wat. Coun. (15), 15

Fish, H., Torrance, S. (1978) Int. Wat. Supply Assoc., Kyoto, Japan pp N11–N19

King, E. F. (1981) Notes on Water Research No. 28 'Biodegradability Testing', Water Research Centre, Medmemham (August, 1981)

Küpfer, A., Al-Dabagh, S. G., Ritchie, J. C., Idle, J. R., Smith, R. L. (1982) Biochem. Pharmacol. 31: 3193

Millard, B. J., Sheinin, E. G., Benson, W. R. (1980) J. Pharm. Sci. 69: 1177–1179

Nicolson, N. J., Casapieri, P., Richardson, M. L. (1981) 'Some Organic Micropollutants in the River Lee Catchment' in Water Quality 1981, Brighton, UK

Richardson, M. L., Bowron, J. M. (1983) Notes on Water Research, No. 32, 'Catchment Quality Control', Water Research Centre, Medmenham, (January 1983)

Siegel, B. B. (1959) Bull. Wld. Hlth. Org. 21: 703–713

Waggott, A. (1981) 'Trace Organic Substances in the River Lee' in Cooper, W. J. (ed.) Chemistry in Water Reuse, Ann. Arbor Publishers Inc. pp 55–99

Wal, J.-M., Bories, G., Manas, S., Dray, F. (1975) FEBS Letters 57: 9–13

Watts, C. D., Craythorne, M., Fielding, M., Steel, C. P. (1983) Identification of Non-volatile Organics in Water Using Field Desorption Mass Spectrometry and High Performance Liquid Chromatography, pp 120–131. Presented at the 3rd European Symposium on Organic Micropollutants, Oslo, Norway, September 19–21, 1983. EEC. In 'Analysis of Organic Micropollutants in Water', (ed.) G. Angeletti and A. Bjørseth, D. D. Reidel Publishing Co. – Dordrech

Wood, L. B., Richardson, M. L. (1978) Chem. in Brit. 14: 491

Wood, L. B., Richardson, M. L. (1980) Prog. Wat. Tech. 12: 1–12

APPENDIX—*see over*

Appendix 1. Pharmaceutical data summary. This indicates paediatric dose data where available and the maximum adult dose for each of the drugs considered. In addition, the *predicted* concentration in the River Lee of most of the drugs is given in μg litre^{-1}; these concentrations were obtained by taking the usage data from general practitioners' prescription information obtained from the National Health Service for 1976–7. From the predicted concentration data the I_{70} figures (mg) were calculated by assuming a person would consume 2 litre of water day^{-1} for 70 years. Other information used in making risk assessments for the pharmaceutical chemicals considered in depth in this study included metabolism, the possibility of the drug crossing the human placenta, secretion into maternal milk, plasma half lives ($P\frac{1}{2}$) (see footnotes).

Acebutolol	AD 400 mg, RL 0·29, I_{70} 15, M1Ac.
Acintirazole	Now only used in veterinary medicine, e.g. fish farming, see text.
Allopurinol	PD 20 mg kg^{-1}, AD 600 mg, RL 0·59, I_{70} 30, M1OH, $P\frac{1}{2}$ 2 h; $P\frac{1}{2}$ 25 h—for alloxanthine.
Aloes	AD 200 mg (proprietary use—no total tonnage data available), DAP, S, not recommended for nursing mothers.
Aminophylline	PD 25 mg up to 1 yr, AD 500 mg, RL 1·02, I_{70} 52·5, M1NdM; Ox, DAP, $P\frac{1}{2}$ 3–9 h.
Amitriptyline	PD not recommended, AD 150 mg, RL 0·88, I_{70} 45, M1OH; NdM, M11 gluc, $P\frac{1}{2}$ 9–76 h (N-oxide formation), non-biodegradable.
Amoxycillin	PD 125 mg up to 10 yrs, AD 1·0 g, RL 1·9, I_{70} 97, DAP, S (allergen?—see text).
Ampicillin	PD 62·5–125 mg up to 1 yr, AD 6·0 g, RL 7·9, I_{70} 403, M1OH, DAP, S, (allergen see text), 48% biodegradable in SCAS test, see text.
Amyl-*m*-cresol	Proprietary use—no tonnage data, low toxicity.
Amylo-barbitone	AD 200 mg, RL 1·75, I_{70} 90, M1OH; NOH; Ox, DAP, S, $P\frac{1}{2}$ 20 h.
Aspirin	PD 75–150 mg 1–2 yrs, AD 8·0 g, RL 14·6 (161 if 1000 tonnes proprietary inc.), M1OH, M11 gluc; gly, readily degradable (see text).
5-Azacytidine	Antineoplastic agent, soln unstable.
Azathioprine	M11glut, $P\frac{1}{2}$ 24 h (mutagen and antimetabolite).
Benorylate	PD 25 mg kg^{-1} up to 1 yr, AD 8·0 g, RL 9·2, I_{70} 470 (readily hydrolysed to paracetamol and acetylsalicylic acid).
Benzathine penicillin	PD <300 mg for 6–12 yrs, AD 1·8 g, RL 0·29, I_{70} 15 (converts to benzylpenicillin and benzathine).
Benzocaine	PD not recommended, AD 200 mg, RL 0·15, I_{70} 7·5, M1Hyd (mainly external application).
Benzyl benzoate	RL 1·32, I_{70} 67·5, M1Hyd, M11gly (forms benzoic acid—external application).
Benzylpenicillin	PD 0·5–1·0 g, AD 6·0 g (max 24·0 g), RL 0·15, I_{70} 7·5, DAP, $P\frac{1}{2}$ 30–160 min.
Bismuth subgallate	RL 0·15, I_{70} 7·5 (external application).
Butaphyllamine	PD not recommended for <5 yr old, AD equiv. 800 mg theophylline, RL 0·15, I_{70} 7·5, M1NdM, see also theophylline.
Butobarbitone	AD 200 mg, RL 1·17, I_{70} 60, M1Ox, DAP, S, $P\frac{1}{2}$ 55 h.
Caffeine	AD 300 mg, RL 0·29, I_{70} 15, M1NdM; Ox, S, $P\frac{1}{2}$ 4–10 h, readily biodegradable, found in sewage, rivers and present in beverages, see text.
Carbamazepine	PD 600 mg up to 12 yrs, AD 2·2 g, RL 0·44, I_{70} 22·5, M1OH; Ox, M11gluc, DAP, S, $P\frac{1}{2}$ 21–53 h (epoxide formed?).
Carbocisteine	PD 500 mg for 2–5 yrs, AD 2·2 g, RL 0·44, I_{70} 22·5, M1S-OX.
Carbromal	PD not recommended, AD 1·0 g, RL 0·29, I_{70} 15, M1OH.
Carmustine	Alkylating agent, small usage, $P\frac{1}{2}$ 15 min.
Cephalexin	PD 50 mg kg^{-1}, AD 4·0 g, RL 0·59, I_{70} 30, DAP, S, $P\frac{1}{2}$ 0·5–2 h.
Chlor-diazepoxide	PD 20 mg, AD 60 mg, RL 0·29, I_{70} 15, M1OH; NdM, M11gluc, DAP, S, $P\frac{1}{2}$ 6–28 h.

continued

Key

PD = Paediatric dose
AD = Adult dose
RL = River Lee μg litre^{-1}
I_{70} = Ingestion for 70 yrs (mg)
M1 = Phase 1 metabolism
M11 = Phase 11 metabolism (conjugation)
DAP = Drug crosses placenta
S = Secreted into mother's milk
$P\frac{1}{2}$ = Plasma half life

Ac = Acetylation
dAc = Deacetylation
deC = Decarboxylation
Hyd = Hydrolysis
NdM = *N*-demethylation
NOH = *N*-hydroxylation
NM = *N*-methylation
Nox = *N*-oxidation
OdM = *O*-demethylation
OH = Hydroxlation
OM = *O*-methylation
Ox = Oxidation
OxD = Oxidative deamination
S-OX = *S*-oxidation

cyst = conjugation with cysteine
gluc = conjugation with glucuronide
glut = conjugation with glutathione
gly = conjugation with glycine
SO_4 = conjugation with sulphate

Chlorhexidine	AD 2·0 g (human metabolic experiment), can hydrolyse to form 4-chloroaniline, proprietary preparation—no usage data available, non-biodegradable.
Chlormethiazole (edisylate)	PD not recommended, AD max 8·0 g, RL 0·44, I_{70} 22·5, M1OH; Ox, DAP, $P\frac{1}{2}$ 4 h, dechlorinates.
Chlormezanone	AD 800 mg, RL 0·29, I_{70} 15, M1Ox; Hyd.
Chloroform	Use restricted see Statutory Instrument 1979 No 382, WHO Drinking Water Guidelines 30 μg litre^{-1}.
Chlorothiazide	PD 25 mg kg^{-1}, AD 2·0 g, RL 0·15, I_{70} 7·5, DAP (very little metabolism).
Chlor-promazine	PD <80 mg for 6–12 yrs, AD 200 mg, RL 0·29, I_{70} 15, M1OH; NdM; S-OX; Nox, M11gluc, DAP, $P\frac{1}{2}$ 4 h (induces liver enzymes).
Chlor-propamide	AD 500 mg, RL 0·73, I_{70} 37·5, M1OH, hyd, $P\frac{1}{2}$ 25–42 h.
Chlor-tetracycline	PD 20 mg kg^{-1} (only if essential), AD 3·0 g, RL 0·15, I_{70} 7·5, DAP, S, $P\frac{1}{2}$ 5–6 h.
Chlorthalidone	AD 200 mg, RL 0·15, I_{70} 7·5, $P\frac{1}{2}$ 50–90 h (very little metabolism).
Choline salicylate	See Aspirin.
Choline theophyllinate	PD <375 mg for 3–6 yrs, AD 1·6 g, RL 1·02, I_{70} 52·5 (see theophylline).
Cisplatin	Antineoplastic agent—used in small quantities, not recommended in pregnancy, $P\frac{1}{2}$ 25–49 min to 58–73 h.
Clindamycin	PD 24 mg kg^{-1}, AD 1·8 g, RL 0·15, I_{70} 7·5, M1NdM; S-OX, DAP, S, $P\frac{1}{2}$ 2–3 h.
Clofibrate	PD 1·0 g for 10 yr old, AD 2·0 g, RL 6·3, I_{70} 321, M11gluc, non-biodegradable see text.
Clomipramine	PD <30 mg for >5 yrs, AD 150 mg (oral); 50 mg (i.v.), RL 0·15, I_{70} 7·5, M1MdM; OH.
Codeine (phosphate)	PD not recommended up to 6 yrs, AD 60 mg, RL 0·88, I_{70} 45, M1OdM; NdM, M11gluc; SO_4, DAP (codeine, norcodeine or morphine conjugates found—see text).
Crotamiton	RL 0·15, I_{70} 7·5 (external application only).
Cyclandelate	AD 1·6 g, RL 1·02, I_{70} 52·5.
Cyclizine	PD 25 mg for 3–5 yrs, AD 150 mg, RL 0·15, I_{70} 7·5, M1NdM.
Cyclo-phosphamide	Antineoplastic agent used in small quantities, M1OH, DAP, S, $P\frac{1}{2}$ 3–11 h (hydrolyses in water).
Danthron	PD 25 mg, AD 50 mg, RL 0·29, I_{70} 15, M11gluc, S.
Debrisoquine	PD not recommended, AD 300 mg, see text.
Demeclocycline	PD 6 mg kg^{-1} (only if essential), AD 1·8 g, RL 0 15, I_{70} 7·5, $P\frac{1}{2}$ 10–15 h.
Dextro-methorphan	PD 15 mg for 2–4 yrs, AD 30 mg, proprietary usage—hence no tonnage available, M1NdM; OdM, M11SO_4, degrades to morphinan struct. see text.
Dextro-proproxyphene	PD not recommended, AD 520 mg, RL 3·2, I_{70} 164, M1NdM, non-biodegradable.
Diazepam	PD 5 mg kg^{-1}, AD 30 mg, RL 0·44, I_{70} 22·5, M1NdM; OH; M11gluc, DAP, S, $P\frac{1}{2}$ <8 days.
Dichloral-phenazone	PD 270 mg up to 1 yr, AD 1·3 g, RL 0·88, I_{70} 45, M1OH; NdM, M11gluc, $P\frac{1}{2}$ <15 h as trichloroethanol.
Dicoumarol	AD 300 mg, small usage (largely replaced by warfarin), DAP, S, can cause microsomal inhibition.
Diethylpropion	PD 50 mg for 6–12 yrs, AD 75 mg, RL 0·59, I_{70} 30, M1NOH, M11gluc, $P\frac{1}{2}$ 1·5–3 h.
Dihydrocodeine (tartrate)	PD 0·5 mg kg^{-1}, AD 60, RL 0·29, I_{70} 15, DAP.
Dimethicone	PD 100 mg day^{-1}, AD 400 mg, RL 4·4, I_{70} 224, low toxicity, non-biodegradable.
Dioctyl sodium sulphosuccinate	PD 125 mg, AD 500 mg, RL 0·15, I_{70} 7·5, little metabolism.
Diphen-hydramine	PD 200 mg for 6–12 yrs, AD 200 mg, RL 1·02, I_{70} 52·5, $P\frac{1}{2}$ 13–21 h (extensive first pass in liver).
Dithiepin	AD 150 mg, RL 0·29, I_{70} 15, see also diazepam.
Emepronium (bromide)	AD 600 mg, RL 0·29, I_{70} 15, $P\frac{1}{2}$ 2 h (excreted mainly unchanged).
Enheptine	Used in fish farming.
Ephedrine	PD 750 μg kg^{-1}, AD 60, RL 0·44 (also proprietary use), I_{70} 22·5, M1NdM; OxD, M11gluc, $P\frac{1}{2}$ 3–11 h.
Erythromycin	PD 2·0 g day^{-1} for 20 kg child, AD 4·0 g, RL 2·2, I_{70} 112, M11OdM, non-biodegradable.
Ethynyl oestradiol	AD 50 μg, RL 0·003, I_{70} 0·14, see text.
Ethoheptazine	PD not recommended, AD 60, RL 0·73, I_{70} 37·5, extensive metabolism.
Ethylene oxide-propylene oxide	(inert binder)
Fenfluramine	PD 20 mg for 6–10 yrs, AD 120 mg, RL 0·15, I_{70} 7·5, M11gly, DAP, $P\frac{1}{2}$ 11–30 h (forms hippuric acid).
Fenoprofen	PD not recommended, AD 2·4 g, RL 1·61, I_{70} 82, M1OH, M11gluc, S (little), $P\frac{1}{2}$ 2–3 h (phenobarbitone induces metabolism).
Ferrous fumarate	PD 140 mg for up to 6–12 yrs, AD 600 mg, RL 0·59, I_{70} 30.
Flucloxacillin	PD 500 mg up to 2 yrs, AD 2·0 g, RL 0·29, I_{70} 15, $P\frac{1}{2}$ ~50 min (very little metabolism).
Fludro-cortisone	AD 0·3 g, very small usage, $P\frac{1}{2}$ ~30 min, not recommended during pregnancy.
5-Fluorouracil	PD not recommended, cytotoxic agent used in small quantities, AD 15 mg kg^{-1} i.v., $P\frac{1}{2}$ < 3 h.
Flurazepam	PD not recommended, AD 30 mg (100 mg for anaesthesia), RL 0·15, I_{70} 7·5, M1OH (little, M11gluc; SO_4; N-Ac, $P\frac{1}{2}$ ~75 h.
Frangula (chysophanic acid; emodin; frangutin)	RL 1·17, I_{70} 60 (contains <6% glucofrangulins ~0·5 tonne).
Frusemide	PD 3 mg kg^{-1}, AD 400 mg, RL 1·32, I_{70} 67, M11gluc, $P\frac{1}{2}$ 30 min (little metabolism).

Gentian (gentiopicrin, gentisic acid, gentisin)	RL 0·15, I_{70} 7·5 (each <1 tonne).
Glutethimide	PD 125 mg for 1–5 yrs, AD 500 mg, RL 0·59, I_{70} 30, M1OH, S (little), $P\frac{1}{2}$ 5–22 h.
Glyceryl guaicolate (guaiphenesin)	PD 75 mg for 3–12 months, AD 1·6 g, RL 1·02, I_{70} 52·5, M1Ox, $P\frac{1}{2}$ 1 h.
Glycol salicylate	RL 0·29, I_{70} 15, M11gluc, DAP, S (applied externally).
Hexetidine	RL 0·15, I_{70} 7·5 (external application only).
Hydrochlorothiazide	PD 2·5 mg kg^{-1}, AD 100 mg, RL 1·02, I_{70} 52·5, $P\frac{1}{2}$ 3 h (very little metabolism).
Hydrocortisone	PD 6–10 mg kg^{-1}, AD 50 mg, RL 0·15, I_{70} 7·5, M1OH, M11gluc; SO_4, $P\frac{1}{2}$ 100 min (reduction of A-ring, 20-keto reduction).
Hydrotalcite	Inert.
Hyoscyamus (hyoscyamine, hyoscine)	PD 0·6 mg up to 10 yrs, AD 3·0 mg, RL 0·15, I_{70} 7·5, M11gluc.
Ibuprofen	PD max of 500 mg day^{-1} if body weight <30 kg, AD 1·2 g, RL 9·5, I_{70} 486, M1OH; deC; Nox, inherently biodegradable.
Imipramine	PD 30 mg for 6–10 yrs, AD 150 mg, RL 0·29, I_{70} 15, M1OH; NdM; Nox, M11gluc, DAP (rats), $P\frac{1}{2}$ 3–4 h.
Indomethacin	AD 200 mg, RL 1·32, I_{70} 67, M1OdM, M11gluc (also N-deacylation).
Inositol nicotinamide	PD not recommended, AD 1·5 g, RL 3·8, I_{70} 194 (see nicotinamide).
Ipecacuanha	PD not recommended, RL 1·17, I_{70} 60 (contains <2% alkaloids).
Isophosphamide	PD very limited use only, AD max 10 g, cytotoxic drug used in very small quantities, M1OH (hydrolyses slowly in water).
Karaya gum	PD up to 3·0 g day^{-1}, AD 24·0 g, RL 9·2, I_{70} 470 (hydrolyses to form carbohydrates).
Ketoprofen	PD not determined, AD 200 mg, RL 0·44, I_{70} 22·5, M1OH, M11gluc, $P\frac{1}{2}$ 1·5–2 h.
Levodopa	PD not recommended, AD 8·0 g, RL 0·59, I_{70} 30, M1OH; OM; OxD; deC, S, $P\frac{1}{2}$ of 3-O-methyldopa ~13 h.
Levonorgestrel	AD 0·03 g, very limited usage, see text.
Lymecycline	PD 36 mg kg^{-1}, AD 1·6 g, RL 0·15, I_{70} 7·5, DAP, little metabolism.
Lynoestrenol	AD 2·5 g, RL 0·09, very limited usage, see text.
Mebeverine	PD 7 yrs & over—adult dose, AD 400 mg, RL 0·29, I_{70} 15.
Mebhydrolin	PD up to 200 mg for 10 yrs, AD 300 mg, RL 0·15, I_{70} 7·5.
Mefenamic acid	PD 25 mg kg^{-1} day up to 6 months, AD 1·5 g, RL 1 17, I_{70} 60, M1Ox, S (little), some conjugation.
Menthol	PD not for use up to 6 yrs, proprietary use, M11gluc (fatal dose man 2·0 g), readily biodegradable.
Meprobamate	PD not recommended, AD 1·2 g, RL 2·6, I_{70} 134, M1gluc; SO_4, DAP?, S? (to be avoided with nursing mothers), non-biodegradable.
Metformin HCl	AD 3·0 g, RL 0·44, I_{70} 22·5, $P\frac{1}{2}$ 3 h.
Methaqualone	AD 300 mg, RL 0·59, I_{70} 30, M1OH, M11gluc, S (little) $P\frac{1}{2}$ 2–3 h, see text.
Methocarbamol	PD 15 mg kg^{-1} 6 h^{-1}, AD 8·0 g, RL 0·59, I_{70} 30, M1OdM; OH (rat), M11gluc; SO_4, $P\frac{1}{2}$ 1–2 h.
Methotrexate	AD up to 22 g day^{-1}, cytotoxic agent, used in small amounts, see text.
Methyldopa	PD max 65 mg kg^{-1} day^{-1}, AD 3·0 g, RL 17·5, I_{70} 897, M1OM; deC, M11SO_4, non-biodegradable.
Methyl salicylate	See aspirin.
Metronidazole	PD 15 mg kg^{-1}, AD 2·4 g, RL 0·29, I_{70} 15, M1Ox, M11gluc, DAP, S, $P\frac{1}{2}$ 6 h, non-biodegradable under aerobic conditions, see text.
Misonidazole	Neoplastic agent used in very small quantities.
Morphine (morphinan)	See text.
Nalidixic acid	PD 60 mg kg^{-1}, AD 4·0 g, RL 1·02, I_{70} 52·5, M1OH, M11gluc, $P\frac{1}{2}$ 90 min.
Naproxen	PD not recommended, AD 500 mg, RL 2·3, I_{70} 119, M1OdM, M11gluc, DAP, S, non-biodegradable.
Neomycin	PD 80 mg kg^{-1} for 6–12 yrs, AD 3·0 g, RL 0·29, I_{70} 15, $P\frac{1}{2}$ 2 h (only 1–6% absorbed).
Nicotinamide	PD 20 mg kg^{-1}, AD 500 mg,, RL 2·0, I_{70} 105, readily biodegradable, hydrolyses to nicotinic acid.
Nicotinic esters	AD 500 mg, RL 0·29, I_{70} 15, M1Hyd, M11gluc; cyst; gly, hydrolyses to nicotinate; 15–20 mg day^{-1} required by humans.
Nitrazepam	PD 5 mg kg^{-1}, AD 10 mg, RL 0·29, I_{70} 15, M1OH; Ac, M11gluc, S, $P\frac{1}{2}$ 17–28 h.
Nitrofurantoin	PD 6 mg kg^{-1} day^{-1}, AD 360 mg, used in small quantities in human therapy—also used in fish farming DAP, S, $P\frac{1}{2}$ ~20 min, mutagen?
Nitrofurazone	AD 2·0 g, used in small quantities—also in fish farming, mutagen?
Nitrothiazole	Used in fish farming—mutagen?
Norethisterone	AD 400 mg, RL 0·04, I_{70} 2·2, see text.
Nystatin	PD 90 mg, AD 900 mg, RL 0·29, I_{70} 15, poorly absorbed.
Orciprenaline	PD 2·6 mg (inhaled), AD 80 mg, RL 0·15, I_{70} 7·5, M1OM, M11SO_4, $P\frac{1}{2}$ up to several h.
Orphenadrine	PD not recommended, AD 400 mg, RL 0·29, I_{70} 15, M1OxD, NdM; Nox, M11gluc; SO_4, $P\frac{1}{2}$ 14–25 h.
Oxazepam	PD not recommended, AD 180 mg, RL 0·15, I_{70} 7·5, M11gluc, $P\frac{1}{2}$ 4 h.
Oxprenolol	PD <1 mg kg^{-1}, AD 2·0 g, RL 1·46, I_{70} 75, M1NdM, M11gluc, $P\frac{1}{2}$ 80–120 min, extensive first-pass metabolism.
Oxyphenbutazone	PD 10 mg kg^{-1}, AD 400 mg, RL 0·29, I_{70} 15, M1OH, $P\frac{1}{2}$ 27–64 h.

Oxytetracycline	PD up to 30 mg for 2 yrs, RL 6·7, I_{70} 344, see tetracycline.
Paracetamol	PD up to 120 mg for 1 yr, AD 4·0 g, RL 84·1 (but 340 if proprietary use included), I_{70} 4298 (13374), M1OH; OM, M11gluc; SO_4; cys, readily biodegradable after acclimatization.
Penicillin(s) inc. penicillin V	See ampicillin and text.
Pentazocine	PD 50 mg for 6–12 yrs, AD 800 mg, RL 0·29, I_{70} 15, M1Ox, M11gluc DAP, $P\frac{1}{2}$ 2–3 h.
Pentobarbitone	PD not recommended, AD 200 mg, RL 0·59, I_{70} 30, M1OH; Ox, $P\frac{1}{2}$ <50 h, some ring fission and further oxidation.
Phenacetin	PD not recommended, AD 3·0 g,, RL 0·44, I_{70} 22·5, M11gluc; SO_4; glut, $P\frac{1}{2}$ 1–2 h.
Phenbutrazate	PD not recommended, AD 60 mg, RL 1·02, I_{70} 52·5.
Phenethicillin (potassium)	PD 500 mg up to 10 yrs, AD 1·5 g, RL 0·15, I_{70} 7·5, DAP, $P\frac{1}{2}$ 30–50 min.
Phenformin	AD 200 mg, RL 0·15, I_{70} 7·5, M1OH, $P\frac{1}{2}$ <13 h, nearly half excreted unchanged, can cause microsomal inhibition.
Phenobarbitone	PD 60 mg for 12 yrs, AD 350 mg, RL 1·17 I_{70} 60, M1OH, M11SO_4, $P\frac{1}{2}$ 100 h, a major inducer of mixed function oxidase, $P\frac{1}{2}$ less in newborn.
Phenol-phthalein	AD 300 mg, RL 0·15, I_{70} 7·5, mainly excreted in faeces.
Phenylbutazone	PD 5–10 mg kg^{-1}, AD 400 mg, RL 1·61, I_{70} 82, M1OH, $P\frac{1}{2}$ 1–7 days, no conjugates.
Phenylephrine	PD up to 6 yr not recommended, AD 50 mg, proprietary composition.
Phenylpro-panolamine	PD 15 mg for 3–5 yrs, AD 150 mg, RL 0·29, I_{70} 15, 10% degrades to hippuric acid in humans, readily biodegradable after acclimatisation, in STW processes; also proprietary use.
Phenyramidol	Little used, can cause microsomal inhibition.
Phenytoin	PD 150 mg up to 3 yrs, AD 400 mg, RL 1·46, I_{70} 75, M1OH; Hyd, M11gluc, S, $P\frac{1}{2}$ 7–40 h (dose-dependent), subject to enterohepatic circulation.
Piperazine	PD 750–2000 mg up to 2–4 yrs depending on infection, AD 4·0 g, RL 0·15, I_{70} 7·5, excreted unchanged.
Poloxamers	Inert binder.
Prenylamine	PD not recommended, AD 300 mg, RL 0·15, I_{70} 7·5, $P\frac{1}{2}$ 7 h.
Primodone	PD 750 mg up to 3–5 yrs AD 2·0 g, RL 1·32, I_{70} 67, M1OH; Ox; deC, S, $P\frac{1}{2}$ 3–25 h.
Prochlor-perazine	PD 5 mg up to 1–5 yrs, AD 100 mg, RL 0·15, I_{70} 7·5 $P\frac{1}{2}$ 10–30 h, rats: ring fission, N-dealkylation.
Progesterone	AD 60 mg (intramuscular injection), small use, M11gluc, $P\frac{1}{2}$ few min, see text.
Promethazine	PD 10 mg up to 1 yr, AD 50 mg, RL 0·15, I_{70} 7·5, M1Ox, M11gluc, S, $P\frac{1}{2}$ 4 h, high first-pass metabolism.
Propranolol	PD 1 mg kg^{-1}, AD 2·0 g, RL 1·61, I_{70} 82, M1OH; OxD; NdM, M11gluc; SO_4, DAP, 2, 2–4 h, high first-pass metabolism.
Pseudophedrine	PD 45 mg up to 1 yr, AD 180 mg, RL 1·17, I_{70} 60, M1NdM, $P\frac{1}{2}$ 5–8 h, 98% excreted unchanged.
Pyridoxine HCl	AD 300 mg, RL 0·15, I_{70} 7·5, pyridoxic acid mainly excreted.
Quinal-barbitone	AD 250 mg (pre-med); 100 mg (hypnosis), RL 0·73, I_{70} 37·5, M1OH, Ox, DAP, S, $P\frac{1}{2}$ 29 h.
Quinidine	AD 3·0 g, RL 1·61, I_{70} 82, $P\frac{1}{2}$ 6–7 h, ~50% excreted unchanged.
Riboflavine	AD 10·0 mg, RL 0·15, I_{70} 7·5, DAP, S, rapidly metabolised.
Rutoside	AD 300 mg, RL 0·29, I_{70} 15.
Salbutamol	PD 0·8 mg (inhaled), AD 16 mg, RL 0·15, I_{70} 7·5, $P\frac{1}{2}$ 2–7 h, high first-pass metabolism.
Salicylamide	See aspirin.
Salicylic acid	See aspirin—external application, RL 0·29, I_{70} 15.
Sodium actal	Inorganic hexitol complex—biodegradable.
Sodium chomoglycote	AD 120 mg (inhalation), RL 0·29, I_{70} 15, $P\frac{1}{2}$ 80 min, excreted unchanged—more in faeces than urine.
Sodium poly-hydroxl-aluminium monocarbonate-hexitol complex	RL 1·32, I_{70} 67.
Sodium valproate	PD 20 mg kg^{-1} up to 20 kg, AD 2·0 g, RL 0·29, I_{70} 15, M1Ox, M11gluc, S, $P\frac{1}{2}$ 6–16 h.
Sparteine	AD 600 mg, small use, can cause microsomal inhibition.
Spironolactone	PD 3 mg kg^{-1}, AD 400 mg, RL 0·29, I_{70} 15, M11gluc, S (competitive inhibititor of aldosterone-thioacetyl group is readily removed forming canrenone, which is found in milk)
Sulpha-guanidine	AD 10·0 g, RL 0·29, I_{70} 15, M1Ac, $P\frac{1}{2}$ 2 h.
Sulpha-methizole	AD 1·2 g, RL 0·29, I_{70} 15, M1Ac (converted to sulphonamide).
Sulpha-methoxazole	PD 200 mg day^{-1} in 5 + 1 ratio with trimethoprim, AD 2·4 g, RL 7·2, I_{70} 366, M11Ac, non-biodegradable.
Sulpha-phenazole	AD 2·0 g, can cause microsomal inhibition.
Sulphasalazine	PD <150 mg kg^{-1}, <3.0 g for 20 kg child, AD 12·0 g, RL 1·8, I_{70} 90, M1OH, M11gluc, non-biodegradable (undergoes azo reduction in the human intestine).
Synthetic steroids	See text.
Tetracycline	PD 10–50 mg kg^{-1} day^{-1}, for 20 kg = 1·0 g/day (stains teeth), AD 3·0 g, RL 2·9, I_{70} 149, DAP, S, non-biodegradable.
Tetrahydro-furfuryl (salicylate)	RL 0·29, I_{70} 15, applied externally.
Theobromine	PD not given, AD 900 mg, RL 0·29, I_{70} 15, M1NdM, readily biodegradable.

Theophylline	AD 700 mg, redily biodegradable.
Thiamine	AD 100 mg, RL 0·44, I_{70} 22·5, S.
Thioridazine	PD 1 mg kg^{-1}, AD 600 mg, RL 0·15, I_{70} 7·5, M1OH, M11gluc, DAP, $P\frac{1}{2}$ 9–10 h (similar to chlorpromazine metabolism, may persist up to 1 yr).
Thuryl salicylate	External application only, see aspirin.
Thymoxamine	PD not recommended, AD 480 mg, RL 0·15, I_{70} 7·5, M1dAc.
Thyroxine	AD 0·3 mg, RL 0·15, I_{70} 7·5, DAP, $P\frac{1}{2}$ 6–7 days (enterohepatic circulation—normally produced by thyroid gland).
Tolbutamide	PD not recommended, AD 2·0 g, RL 2·2, I_{70} 112, M1deC, S, non-degradable (not recommended in pregnancy), also see text.
Trimethoprim	AD 1·5 g, RL 1·46, I_{70} 75, M1OH; OdM; Ox, M11gluc; SO_4, DAP, $P\frac{1}{2}$ 11–17 h.
Trimipramine	PD not normally given, AD 150 mg, RL 0·15, I_{70} 7·5 (extensive metabolism).