Discussion

Histopathological and functional lesions of the thyroid gland are usually effected either by thyromimetic agents (feedback inhibition of pituitary TSH output leading to thyroid inactivity and follicular cell atrophy) or agents which lower circulating thyroid hormones (feedback stimulation of TSH output leading to thyroid hyperactivity and non-genotoxic promotion of thyroid cell growth; see Zbinden 1987; Atterwill & Brown 1988).

Our data support the findings of Ekman et al (1985) who reported that high doses of omeprazole (138–414 mg $kg^{-1}day^{-1}$) decreased plasma T_3 concentrations, and lowered 5′-deiodinase activity in liver homogenates. We have shown that high doses of omeprazole (up to 500 mg kg^{-1}) appear to inhibit peripheral 5′-deiodinase activity and cause some decreases in plasma T_3 concentrations, particularly in male rats. Little or no reductions in circulating T_4 were found showing that omeprazole probably does not directly inhibit thyroxine biosynthesis (i.e. peroxidase activity). This was supported by only a very weak in-vitro action on iodide organification in cultured porcine thyrocytes. Omeprazole was much less potent in this respect than the directly acting goitrogens PTU and methimazole (100–200 fold more potent than omeprazole). Furthermore, no effect on radioiodide uptake or organification in the rat thyroid gland in-vivo could be detected using the perchlorate discharge test, using high doses of omeprazole which inhibited peripheral deiodinase activity. Additionally, omeprazole did not appear to cause feedback stimulation of TSH output by increasing thyroxine clearance as do many compounds such as phenobarbitone and SK&F 93479 (Brown et al 1987).

These data indicate that the small rises in serum TSH in response to lowered circulating T_3 concentrations induced by subacute omeprazole treatment at toxicological doses are not sufficient to markedly affect functional aspects of thyroid follicular cell function as measured by iodide accumulation and organification in-vivo. In conclusion, therefore, omeprazole appears to have weak effects on the pituitary–thyroid–liver axis, its main action being to inhibit the peripheral deiodination of thyroid hormones. It seems to have only a very weak potential to directly inhibit thyroid hormone synthesis as shown in-vitro using cultured thyroid cells. The net effect of these actions does not appear to enhance TSH stimulation of the thyroid follicles to a level promoting increased functional activity or histopathological lesions.

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The relevance of the presence of certain synthetic steroids in the aquatic environment

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Abstract—Norethisterone and ethinyloestradiol concentrations in sewage effluent, reservoirs, rivers and potable water have been estimated at less than 20 ng L^{-1}, a value unlikely to present a significant risk to human health.

One group of widely used pharmaceutical chemicals to which the public are exposed both in the home and hospital consists of synthetic steroids. An earlier review (Richardson & Bowron 1985) of the Catchment Quality Control (CQC) studies undertaken by the Thames Water Authority (TWA) (Fish & Torrance 1977, 1978; Wood & Richardson 1978, 1980; Nicolson et al 1981; Richardson & Bowron 1983; Bowron & Richardson 1984), highlighted, amongst other groups of pharmaceutical chemicals, the potential public health concern if such chemicals were allowed to enter the aquatic environment and if found to be present in potable water supplies.

The role of immunoassay in the analysis of such microcontaminants in water samples has been described (Aherne 1984, 1987). Immunoassay procedures have been used to determine levels of norethisterone and ethinyloestradiol in various water samples (Aherne et al 1985) and a further set of samples has been analysed in this study. Norethisterone and ethinyloestradiol were chosen as typical synthetic steroids prescribed in significant quantities (Wood & Richardson 1980) and because the specific antisera were available.

Materials and methods

Snap samples of sewage treatment work effluent, rivers, impounding reservoirs and potable water were collected from areas of S.E. England. All sewage works utilized activated sludge processes and were operating at design output. River water

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samples were obtained at medium flow levels. The samples were stored at 4°C until they were concentrated by freeze drying, reconstituted in steroid-free serum and analysed for norethisterone and ethinyloestradiol by immunoassay procedures already described (Turkes et al 1980. Dyas et al 1981). Limits of detection of 2 and 1 ng L^{-1}, respectively, were achieved.

Results and discussion

The results of the analysis are shown in Table 1. Of the two drugs studied norethisterone is prescribed in the larger quantity (approximately five times more than ethinyloestradiol) (Martindale 1982); however, the concentrations found, at least in potable water, were no higher on average than that of ethinyl oestradiol. These findings support biodegradability studies which showed that norethisterone was subject to 28% biodegradation in an activated sludge system in 6 h and was completely degraded in 24 h (Von Rathner & Sonneborn 1979). As a 2 ng L^{-1} concentration is approximately 250000 times less than an average daily dose of norethisterone, a person would need to drink approximately 45000 L of water a day to equate with an average prescribed dose of drug. Hence, there appears to be no risk to the population in drinking such water.

Ethinyloestradiol was unchanged after 120 h in an activated sludge system (Von Rathner & Sonneborn 1979). Taking the worst case from Table 1, a 5 ng L^{-1} concentration in drinking water, (or 10 ng per day), the dose equates approximately to 1:5000 of an average prescribable dose or ingestion of 10000 L of water. Again, there appears to be no risk.

The average daily dose of these synthetic steroids which may arise from ingestion of potable water can be put into context by considering the serum concentrations achieved following administration of the drugs themselves. Peak serum concentrations occur approximately 1 h after norethisterone administration and account for 2–3% of the dose (1 mg). At 24 h, 0·5% of the dose is present in serum. Serum concentrations of ethinyloestradiol range from 2–15 ng mL^{-1} following a 1 mg dose of the drug (Parke-Davis, private communication).

The EEC Scientific Working Group on hormonal substances used to fatten animals (1984) were of the opinion that levels of natural oestrogen in beef, typically found to be in the region of 0·03 $\mu g\ kg^{-1}$ of edible tissue were toxicologically negligible in the human diet. This stance was based on the fact that the daily endogenous production of oestrogen by humans ranged from 1–40 μg in infants, 40–130 μg in men, 50–450 μg in women during reproductive life and 5–40 μg in menopausal women, thus exceeding the amount obtained from the diet by 2 or 3 orders of magnitude. In addition, oral bioavailability is only likely to be 15% of the amount ingested.

Table 1. Results of immunoassay of steroid oral contraceptives in water samples.

	Norethisterone		Ethinyl oestradiol	
	Sept 1982	Aug 1987	Sept 1982	Aug 1987
Samples taken from	ng L^{-1}		ng L^{-1}	
Sewage treatment works effluent (8 samples)	n/u	8–20	n/u	<1–7
Rivers (13 samples)	<10–17	<2–10	<5	2–15
Impounding reservoirs (3 samples)	n/u	<2–10	n/u	1–3
Potable water (12 samples)	<10	<2	<5	<1–4

n/u = not undertaken.

Consequently, oestrogens derived from a water supply containing 0·015 $\mu g\ L^{-1}$ (taking the river water results rather than the potable water results as a theoretical worse case situation), would possibly double the intake from food sources and would still not appreciably increase normal body concentrations. The extent to which concentrations of xenobiotic oestrogens can be compared to those of endogenous steroids is not known, but it would seem that the concentrations measured in potable water are unlikely to present a significant risk to human health.

It is appreciated that whilst norethisterone and ethinyl oestradiol are typical synthetic steroids there are others which are regularly prescribed either singly or in combination, e.g. desogestrel, ethynodiol diacetate, levonorgestrel, lynoestrenol, mestranol, norethynodrel and norgestrel, but it would be an extremely costly and time consuming exercise to measure all these compounds by immunoassay as specific antisera are not yet generally available. However, in view of possible differences between these compounds in their receptor effects, continuing investigations of the amounts of various synthetic steroids in water supplies are necessary so that more specific risks might be assessed.

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