ed from asthma and skin
r, Ann. Allergy 1970,
(Withers & Eale, ibid
at be treated with
and it is difficult
ermine in the welter
ring in even reputable
een food intolerance
y. Some children, for
ficit of an intestinal
for milk complex of
ficiencies are the latent
diarrhoea following the
tolerance appears later
and seems to be some
sians (Sharp & Pickles,
stinal cramp and eczema
hypersensitivity to milk
n

s acids may have more
ans processed by bacterial
se intestines. Lactose
ose retain the active
ose retain for the active
ar acid is prac
results in elevated
29, 2)
s. Intolerance
ys or children
terance was suppressed
lonic defect right side
due to milk in them is an

tosorrhoea in adults are
ive fat, vitamin
, etc. [illegible] (Anti-
the pla[illegible] intolerance of
h [illegible]
[illegible]
[illegible]

but antibodies to various stanches have been found in normal persons and, in large amounts, in patients whose condition improved after the removal of the relevant stanch from their diet (Lietta, J. Asthma Res. 1969, 7, 25). Patients sensitive to penicillin react to penicillin residues present in milk (Asher et al. J. Am. Med. Ass. 1969, 207, 145) and cases of allergic reactions to tetracycline and other food dyes have been reported (BIBRA Bull. 1971, 10, 74).

In the last two decades, much has been learnt about food intolerance due to a whole variety of causes, be it an allergy or to enzyme deficiency. The picture is sometimes confused because of the similarities in symptoms or the possible overlap of the two conditions. Such duplication should not delay consideration of what is likely to be a simple dietary problem. Individuals suffering from an acute attack of asthma or eczema as a young child to milk irritation as an adult, and the offending food may be difficult to trace or, less frequently, may be as obvious as illness's sensitivity to fish. Many children recognise the food they are allergic to better than do their mothers. Very young's tantrums and refusal to eat her dinner of lovely pink yummy may well have been due to an instinct for self-preservation rather than to mere temper.

# ARTICLES OF GENERAL INTEREST

## IF ALL THE S[illegible] WERE FOR...

The polychlorinated biphenyls (PCBs) have now well and truly [illegible] up with DDT and mercury in the series of materials recognised as [illegible] environmental contaminants. The publication for membership of [illegible] from more scientific publications, substantial harm to [illegible], and, more importantly, [illegible] from [illegible] the PCBs seem well on all [illegible] [illegible] of the publication [illegible] of serum antibiotic [illegible] of the [illegible] of the pollutants [illegible] a particular or no [illegible] (Nature, [illegible] 10, [illegible], [illegible] 1970, [illegible] 1, 10, [illegible] 50, 51, [illegible], Science, [illegible] 1970, [illegible] 169, [illegible], New Scientist [illegible] 1971, 50, 10).

In all the cases, the [illegible] seem to be of a [illegible], and [illegible] [illegible] [illegible]

of PCBs in the US and the UK, to restrict PCB sales to those destined for use in enclosed applications, such as capacitors and transformers, providing a minimal possibility of leakage into the environment (ibid 1971, 10, 11). As PCBs have been known to cause poisoning in man (ibid 1972, 11, 53; Kuratsune et al Environ Hlth Persp 1971, 66, 1083) and as they are clearly accumulating in the environment from some of the less controllable sources, this decision represents an important advance in reducing the potential hazard proffered by these compounds.

Levels of PCB residues

Aquatic animals and the birds feeding on them are the obvious material to use as a starting point for a survey of PCB contamination. Furthermore, as the PCBs, especially the more highly chlorinated ones, have an extremely low solubility in water, one would expect them to be principally associated with the sediment on the bottom of seas and to enter into food chains via bottom-living organisms.

Practical verification of this theory has come from Escambia Bay, Florida, where PCB residues of up to 120 and 1·5 ppm have been found in shrimps and crabs respectively (Nimmo et al. Nature, Lond. 1971, 231, 50). The PCBs, which were mainly located in the sediments of the bay, originated from a nearby electrical plant. Samples taken from places [illegible] involving exposure of shrimps and crabs to polluted sediment in the laboratory for 30 days, confirmed that both species were capable of absorbing PCBs from their environment to such an extent that the final residue level in the animals after 30 days often exceeded that in the sediment itself. A [illegible] (Nature, Lond. 1971, 232, 213), using the small shrimp, Gammarus oceanicus. In this case, exposure was for shorter periods [illegible] than 4 days. The uptake of PCBs was found to depend on both the external PCB concentration and the total exposure period, but after 4 hours there was a reduction in the rate of uptake. In another study (Sanders & Chandler, Bull. env. contam. & Toxicol. (U.S.) 1972, 7, 257), eight invertebrate species, including shrimps, crayfish and several types of immature aquatic insect, were exposed to PCB at concentrations below 3 ppb*, a level similar to that found in the waters of Escambia Bay. After exposure for 4 days, total body concentrations varied from 0·2 ppm in crayfish to 16 ppm in the glass shrimp and 92 ppm in daphnia. In road [illegible] exposed to 1·0 ppm PCB, the concentration in the [illegible] reached equilibrium in 14 days and was then 17,500 times [illegible] than the concentration in the water.

As one might expect, the levels found in fish are somewhat less, most commonly in the 0–1 ppm range. In a Canadian survey of fish taken from [illegible], mainly from the sea and reported by Holden (ibid 1971, 6, 44), [illegible] of 0·2–0·4 ppm were most common but levels up to 1·01 ppm were [illegible]. Similar levels were seen in fish [illegible] (Nature, Lond. 1971, 6, 318). [illegible] of 5, [illegible] ppm [illegible] with mean [illegible] 0·4 ppm. Table 1 of [illegible] [illegible] of some 50 or [illegible]

*1 [illegible]

to 200 ppm PCB. Interestingly, after 84 days in non-polluted water, the PCB levels of the whole fish fell by some 75%.

Similar figures have been reported in a review of PCB contamination by Zitko & Choi (Fisheries Research Board of Canada Technical Report no.272, 1971). Once again the levels in fish were generally less than 1 ppm, although occasionally figures as high as 10-20 ppm were recorded from waters near highly industrial areas. In aquatic birds, and especially their eggs, higher levels were found, figures of 1-10 ppm being not uncommon. Fish-eating birds seem to have particularly high PCB levels, occasionally in excess of 100 ppm. Other animals have also been shown to accumulate PCBs. The blubber of grey seals, for instance, commonly contains 10-50 ppm PCB, and one sample was found to have a level as high as 1800 ppm. Of greater importance to man, however, is the finding of up to 3 ppm PCBs in some commercial fish oils and of 0·18, 0·21 and 0·47 ppm in margarines manufactured, respectively, from 100% vegetable oils and 50 and 80% marine oils.

In view of the known environmental contamination, it is not surprising that PCBs are to be found in man. Two samples of adipose tissue analysed by Biror et al. (Bull. env. contam. & Toxicol. (U.S.) 1970, 5, 317) yielded 200 and 400 ppm PCB and further work has detected PCBs at a concentration of 0·103 µg/ml (or 3·5 ppm based on the milk fat) in human milk. In the latter case, fatty tissue was also examined and found to contain 5·7 ppm PCB [illegible]. However, a survey of [illegible] and 47 from cities in Ohio, failed to confirm these findings (Egan et al. Bull. env. contam. & Toxicol. (U.S.) 1971, 6, 5..). While residues of chlorinated hydrocarbon pesticides were present, there was no evidence of PCBs in the milk of any of these women.

## Toxicity of PCBs

The results of Nimmo et al. (loc.cit.) suggest that the threshold of toxicity of the PCBs to fish lies around 1 ppb. The pink shrimp, Penaeus duorarum, seems equally sensitive (Nimmo et al. Trans. Am. Fish. Soc. 1971, 11, 191). The adults were killed within 17-55 days by Aroclor 1254 concentrations of from 2·4-4·9 ppb, but the juvenile shrimps were found to be less resistant and failed to tolerate even 1 ppb. There were indications that a similar increase in susceptibility to PCBs occurred during moulting. Accumulation (up to 510 ppm) occurred in the hepatopancreas of the animals but subsequently the material was transferred to other tissues and eventually lost. There was very little mortality of [illegible] but [illegible] PCBs was recently reported (Nimmo et al., Mar. Biol. 10, 1, 2-3, (1; Duncan, Fish. Bioassay [illegible] 1971, 1, 1-10) and it is possible that this may also occur in wild populations and deserves further study.

The effects of PCB poisoning are more apparent in birds. For example, chicks fed a diet containing [illegible] presumably [illegible] 10% (Nimmo et al., 1971.) [illegible] 5 [illegible] 3 [illegible] Canada [illegible] [illegible] [illegible]

body weight, an increase in liver weight and an accumulation of PCB principally in adipose tissue, kidney, liver, brain, muscle and blood (Platonow & Funnell, Can. J. comp. Med. 1972, 36, 89). Tissue levels increased linearly with time. Behavioural effects have been seen in caged robins receiving as little as 5 µg PCB (Clophen A50) daily, however. After 20 or so days of treatment, the experimental birds were significantly more active than the control and residue levels in breast muscle ([illegible]) were four times higher (Ulfstrand et al, Nature, Lond. 1971, 231, 467).

Other effects of PCBs in birds include an increase in susceptibility to viral hepatitis seen in ducks challenged with the virus 5 days after the termination of a 10-day course of feeding with diets containing 25-100 ppm Aroclor 1254 (Friend & Trainer, Science, N.Y. 1970, 170, 1314). In pigeons and quails fed wheat dressed with 250-500 ppm Aroclor 1242 or 1254 for 20-28 days, residue levels have been found varying from over 100 ppm in fat to less than 10 ppm in heart and brain (Bailey & Bunyan, Nature, Lond. 1972, 236, 34). The most important result of this work, however, was the finding that PCBs with a relatively low degree of chlorination are fairly rapidly [illegible] disposed [illegible] more highly [illegible] arises that the less widely used compounds, the highly chlorinated PCBs, are more common in the environment than their technologically more popular relations.

The metabolism of an orally administered PCB with a fairly high mean chlorine content (Aroclor 1254) has been studied in the rat by Grant et al. (Bull. env. contam. & Toxicol. (U.S.) 1971, 6, 102). The PCB used consisted of six components recognizable by gas chromatography. In line with the results of Bailey & Bunyan (loc. cit.), tissue residues of the less chlorinated components were significantly lower than the residues of the more chlorinated ones. In addition, total residue figures were increased by treatment of the rats with carbon tetrachloride, a result which, when considered alongside the increase in liver weight observed in this and several other studies, suggests that the liver may be the site of PCB metabolism.

An increase in the activity of the microsomal processing enzymes of the liver has been observed in PCB-treated birds (Bailey & Bunyan, loc. cit.), rabbits (Villeneuve et al. Bull. env. contam. & Toxicol. (U.S.) 1971, 6, 120) and rats (Rickert et al. Arch. Biochem. Biophys. Path. Pharmac. 1972, 3, 505). The more highly chlorinated biphenyls were the most potent inducers, producing a statistically significant and long-lasting effect in both species. Reduction of pentobarbitone sleeping time in rats by a number of PCBs has been shown to increase with the degree of chlorination of the compound and the extent of its storage in fatty tissue (Villeneuve et al. Bull. env. contam. & Toxicol. 1972, 7, 2[illegible]).

[illegible] (Villeneuve et al. 1971, loc. cit.) [illegible] that 10 [illegible] given [illegible] no con- [illegible] to be less [illegible] tive, [illegible] 1971, [illegible] for of [illegible] ering [illegible] acter-

MONS 212412

istic brown discoloration of the skin, especially around the groin, dark-coloured nails and discharging eyes. The condition disappeared within a few months.

An increase in the metabolic activity of the liver is associated with an increase in smooth endoplasmic reticulum (SER). Proliferation of SER and hyaline degeneration have been observed in the livers of PCB-treated mice and [illegible] (Nishizumi, Arch. environ. Hlth 1970, 21, 620). Associated with these effects were disturbances in lipid metabolism and a reduction in liver-glycogen stores.

Similar results have been reported in rabbits following the percutaneous absorption of several PCB preparations (Vos & Beems, Toxic. appl. Pharmac. 1971, 19, 617). Besides liver hypertrophy, damage to the kidney tubules, lymphopenia and atrophy of the thymus were noted. The quantities of PCBs involved, 118 mg applied five times weekly for 38 days, also had a marked effect on the skin. The lesions induced were typified by hyperplasia and hyperkeratosis of the epidermal and follicular epithelia. However, as some PCB preparations produced more severe symptoms than others, the possibility that these effects may have been caused by toxic impurities such as benzofurans must be borne in mind.

[illegible]

Monsanto's recent refusal to sell PCBs for "open" applications and for use in food-processing plants well clearly, in the long term, reduce the potential hazard of these compounds. At present, however, PCBs are present in human food. The levels involved are low—a recent [illegible] estimate put the average daily intake of a person on a high-consumption diet at only 0·1 µg/kg/day (DEPRA Bull. 1972, 11, 169); nevertheless the biological characteristics of the PCBs warrant the continued monitoring of man's exposure to them.

Fish remains man's prime source of PCBs (ibid 1972, 11, 53). Indeed, it is difficult to see how this situation can change in the foreseeable future because, once polluted, the oceans must take a considerable time to recover. Other sources of PCBs can more easily be reduced and eventually eradicated. The finding of PCB residues in poultry and eggs (ibid 1971, 10, 168 & 364) should gradually diminish as PCB-containing meal is removed from the market and the use of biphenyls in food plants is discontinued. Similarly, careful control over the use of PCBs as silo sealants (Shrenkey et al. Bull. env. contam. & Toxicol. (U.S.) 1971, 6, 409) should reduce the possibility of residues in milk. PCBs have been found in the milk of cows fed on [illegible] silage ([illegible] Bull. 1971, 10, 312), and Saschenbrecker (Vet. Rec. 1972, 90, 100) has shown that milk is by far the most important route of excretion of ingested PCB in the lactating cow. After cows have been removed from any PCB contamination, the rate of reduction in the residue level in milk has been found to be similar to that of [illegible] in the [illegible] (Wiese et al. Bull. env. contam. & Toxicol. (U.S.) 1972, 7, 192).

The other [illegible] of dietary PCBs has been food-packaging [illegible] (ibid 1972, 11, 169). [illegible] have stressed that

MONS 212413

alternative solvents are now used (Lister & Bennett, Nature, Lond. 1972, 237, 414).

In the USA, the FDA has set a tentative acceptable daily intake for the PCBs of 150-300 µg (Science, Bull. 1971, 10, 481). The actual daily intake, even before the recent tolerance levels set for various foodstuffs in America (Nature 1972, 11, 1.3), are well below this. As PCB residue levels are unlikely to fall, it seems that man at least should not suffer unduly from the particular environmental hazard. The effect of PCBs on oceans, lakes and rivers and their flora and fauna may be another question.

## TOXICOLOGY'S NEED FOR NEW ANALYTICAL METHODS

At the present time, one of the major problems facing toxicologists is the fact that many of the methods available for analysis of hazardous substances lack either specificity or sensitivity. The purpose of this article is to highlight the problems that arise in establishing chemical identity and quantity in the analysis of toxic substances, to indicate some areas in which improvements may be made, and to suggest some basic approaches that might produce fruitful results.

These topics may be suitably introduced by reference to the comments of a lecturer at a recent meeting in Boston arranged by the American Chemical Society (Eric Uhlenhuth, Int. Drug., 12 (4), 44). Dr. F. Isaacberg of the Massachusetts Institute of Technology is reported as having emphasized the need for new methodological approaches, and particularly for new techniques for the detection of various nitrosamines and their derivatives in a wide variety of foods. He continued by criticizing the lack of specific analytical methods and the low instrumental sensitivity that characterized [illegible] earlier work in this field, and made a plea for the wider application of mass spectrometry to the problem of nitrosamine detection.

The use of the mass spectrometer coupled to the gas-liquid chromatograph (GLC-MS) is indeed one of the most powerful analytical procedures currently available for the detection of organic compounds, and is used by [illegible] laboratories to detect traces of toxic substances down to $10^{-9}$ g (1 nanogram) quantities. [illegible] structure [illegible], the use of this powerful [illegible] and [illegible] in the measurement of [illegible] for example, in a recent review of the use of mass [illegible] Millard (Proc. Soc. Anal. Chem., 1971, 8, 157) [illegible] to the field of [illegible] for toxicology, [illegible] it is [illegible] to [illegible] GLC-MS and [illegible] [illegible] [illegible]