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Review of potentially harmful substances: Carcinogens

WORLD HEALTH ORGANIZATION

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IMO/FAO/Unesco/WMO/WHO/IAEA/UN/UNEP
Joint Group of Experts on the Scientific Aspects of
Marine Pollution
(GESAMP)

REVIEW OF POTENTIALLY HARMFUL SUBSTANCES - CARCINOGENS

WORLD HEALTH ORGANIZATION
Geneva, 1991

NOTES

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"Pollution means the introduction by man, directly or indirectly, of substances or energy into the marine environment (including estuaries) resulting in such deleterious effects as harm to living resource, hazards to human health, hindrance to marine activities including fishing, impairment of quality for use of sea water and reduction of amenities".

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EXECUTIVE SUMMARY

There have been many suggestions that cancers in fish and other marine organisms are commonplace and are attributable to chemical pollution. There is also concern that, as a number of known carcinogens are accumulated by marine organisms that are commercially exploited for human food, they may present a risk to man.

A critical review of the European and North American literature concerning cancer in fish and shellfish shows that, although there are indeed many reports of "cancers" and "precancerous" lesions in fish and shellfish, there is considerable evidence to suggest that due to improper use of terminology, some of the reports are erroneous or misleading. There is strong circumstantial evidence, especially from North America, that polycyclic aromatic hydrocarbons and a few other hydrocarbons may cause liver cancer in fish and shellfish. However, there is very little unambiguous evidence to suggest that other cancers in fish are associated with chemical contaminants. Although the adverse effect on individual fish is undisputed, the review identifies no basis for concern for the survival of marine fish populations, even at local levels, due to carcinogens in the marine environment.

From a human health standpoint, at normal levels of consumption and contamination, the data on consumption of potential carcinogens via marine fish and shellfish give little reason for concern in relation to most of the substances considered. However, there may be increased risks to high seafood consumers in cases where the ingested seafood is abnormally contaminated with carcinogens, particularly PAHs.

Therefore, there is a need for continued vigilance and controls over the disposal of known carcinogens into the environment. More research is necessary to establish cause and effect relationships between carcinogens and marine species. Thus far it is assumed that only chemicals which induce cancer in terrestrial mammals are likely to be the causative agent of cancers in marine organisms. This may or may not be correct.

The review suggests that discharges of carcinogens into the marine environment should be kept as low as possible, taking into account technical and economic circumstances. The present risk is small but the potential one is real enough to predicate the restrictions currently applied to carcinogens in general, and to those specifically identified in this review as potential carcinogenic agents, in particular.

INTRODUCTION

Among the very large number of chemicals used by man, many are released to the environment, either as a result of human activities or as a result of natural processes. A number of these chemicals are clearly recognised as being capable of causing cancer in man, usually through occupational exposure. Other chemicals have been shown to cause cancer in animals exposed under laboratory conditions and these substances, by inference, may be capable of causing cancer in humans. A rather larger number of chemicals is known to be mutagenic and/or teratogenic, especially at high exposures under laboratory conditions. Clearly the use and release to the environment of any such chemicals needs to be very carefully regulated in order to minimise the risk of harmful exposure.

Most of the internationally-agreed Conventions that seek to regulate the disposal of wastes into the marine environment contain general clauses stating that, as a matter of principle, discharges of carcinogens should not be made into the marine environment. However, the question of what substances are to be regarded as carcinogens and why has not been seriously addressed by any of the Regulatory Commissions and so the position remains unclear. Such uncertainties do little to allay public concerns.

At the specific request of IMO, supported by WHO, UNEP and FAO, GESAMP agreed at its Fifteenth Session to investigate the extent to which carcinogenic substances in the marine environment present a risk to aquatic organisms and/or man and need further regulation. There are two possible causes for concern; the first relates to the impact of carcinogens directly on marine organisms; the second relates to the possible impact on man via exposure to carcinogens in the marine environment. Since the levels of all such substances in the marine environment are very low, direct exposure of man is assumed to be insignificant and indirect exposure via marine organisms consumed as food is the only exposure pathway that needs to be addressed. However, because man is exposed to carcinogens by a variety of other routes including other foods, the exposure via seafood needs to be put in this context.

In order to keep the task to one of manageable proportions and recognising that, at least in public perception terms, carcinogens give rise to great concern, it was decided initially to defer reviews of mutagens and teratogens until after completion of the review of carcinogens. The review was conducted under the auspices of a Working Group charged with the Review of Potentially Harmful substances. Most of the work was carried out by correspondence between the working group Chairman, Dr John Portmann, and the main co-sponsoring agencies (Unesco, IMO and WHO) and individual experts:- Mr D Bucke reviewed the European literature and position in relation to the impact of carcinogens on marine organisms, Dr J A Couch produced a similar review of the North American situation. Drs Grasso and Mann of the Robens Institute, United Kindgom, carried out an assessment of the probable risk to humans. This assessment was based on data on contaminant levels in marine organisms collected by the Plymouth Marine Pollution Information Centre (United Kingdom), and on initial assessments of human health risk carried out by Dr L Friberg and Dr L Magos.

A. CANCER IN FISH AND SHELLFISH: A CRITICAL REVIEW OF THE STATUS IN EUROPEAN AND NORTH AMERICAN WATERS

1. General Introduction

Cancers and cancer-like diseases in fish and shellfish have interested biologists and comparative pathologists since the middle of the last century (Bucke, 1988), mainly because the histological characteristics were similar to conditions occurring in mammals, including man. More recently the occurrence of higher incidences of the cancer in fish and shellfish has implicated anthropogenically derived contaminants as possible causative agents. The literature fish cancers has been the subject of several reviews and Symposia proceedings (Schlumberger & Lucke, 1948; Mawdesley-Thomas, 1975; Dawe & Harshbarger, 1975; Peters, 1984; Kraybill et al., 1977; Hoover, 1984; Masahito et al., 1988). There are similar reviews on other aquatic animals (Pauley, 1969; Sparks, 1972; Lauckner, 1983). Critical reviews of the literature to test the claims for the cause of cancerous conditions by pollutants, have also been published (Couch & Harshbarger, 1985; Mix, 1986). There are also a number of carefully selected reviews dealing with specific subjects such as liver tumours in rainbow trout Oncorhynchus mykiss (Hendricks, 1982), or controversial issues such as X-cell tumours in flatfish and gadoids (Dawe, 1981).

The earlier reports of cancers in fish and shellfish were mostly documentations of isolated occurrences, sometimes illustrated with line drawings of the gross and microscopical appearances, and there was little attempt to study the aetiology of these conditions. The first classical studies of cancer in fish began with the identification of "hepatoma" in hatchery-reared rainbow trout, Oncorhynchus mykiss, in the 1960s.

In Europe, systematic studies on the effects of chemicals on fish livers have lagged behind those of North America. That is surprising considering the first record of rainbow trout "hepatoma" (Syn. hepatocellular adenoma and hepatocellular carcinoma) was first reported in the United Kingdom (Haddow & Blake, 1933) and an outbreak of this condition in hatchery-reared rainbow trout spread through parts of Europe in the late 1950's (Levaditi et al., 1960; Ghittino & Ceretto, 1962; Ghittino, 1963).

The cause of the condition was suspected to be dietary related. This suspicion was supported by workers investigating similar problems in trout hatcheries in Japan (Honma & Shirai, 1959) and the United States (Ashley & halver, 1963). However, it was from the United Kingdom that the initial breakthrough came, when investigations into the cause of similar problems in turkeys, ducklings and pheasants revealed that Brazilian groundnut meal had been included in the birds' feed (Blount, 1961; Asplin & Carnaghan, 1961). Subsequently, the liver changes in these birds were shown to be due to the compound 'Aflatoxin', a toxic factor produced by a contaminting mould Aspergillus flavus in the groundnuts (Sargeant et al., 1963). Furthermore, it was shown by Lancaster et al., (1961) that Aflatoxins induced neoplasia in the livers of laboratory animals. From that recognition, workers in the United States realized that groundnuts in trout diets were contaminated with Aflatoxins, and it was these diets that were the cause of hepatic tumours in rainbow trout (Halver, 1967). From there, several research groups pursued studies involving tumour induction in teleost species, especially the rainbow trout. This literature has been thoroughly reviewed by Hendricks (1982).

Probably, the more rapid research progress in North America came because its fast explanding fish-farming industry had caused a demand to replace wet-diets by dry-diets in the 1960's, whereas in Europe, the fish-farming industry was slower to expand, and many farmers were still using wet-diets.

Apart from the hepatic neoplasia of rainbow trout, there have been few authenticated cases of actual cancer epizootics in fish, (Mix, 1986). Most of the examples of cancers and cancer-like conditions in fish and shellfish reported in the past 20 years have been documented by accessions in the Registry of Tumors in Lower Animals (RTLA), Smithsonian Institution, Washington DC, USA (Harshbarger et al., 1989). Almost all the accessions in the RTLA are examples of idiopathic conditions with unknown aetiologies, and, where causal effects have been sought, investigations have

been hampered because of the presence of other factors which could, either, singly, or in any combination, have been responsible for the effects. For example over the past 100 years examples of wart-like growths, especially in certain flatfish species, have been frequently observed and identified as cancerous lesions "caused by pollution". However, when Lowe (1874) and Sandeman (1892), among others, first described such conditions, there was good reason for their naivety because they were confronted with tumour-like lesions but did not have either the technical equipment or knowledge to make an accurate diagnosis. At that time, cancer was an all-embracing term and many pathological conditions fitted into that category. We now know that the disease they described was lymphocystis, a disease which has a definitive viral aetiology (Wolf, 1984). This condition is highly infectious to certain fish species, especially where they occur in dense populations, and it has been endemic for many years in certain areas of the North Atlantic, viz. Liverpool Bay (Johnstone, 1906).

1.1 Definitions

As in the early days, the loose etymology of 'tumours' and 'cancer' is often the cause of misunderstanding and may contribute to much of the controversy and concern that exists. Many reports in the literature are published by scientists who do not have a thorough grounding in histopathology and their incorrect use of terms is often seized upon by the media and the problem compounded. It is important therefore to clarify certain terms from the outset and to use them consistently.

The most widely-used terms associated with "cancer" are "neoplasm" and "tumour" (tumor). In the accepted context of cancer pathology (oncology), "tumour" is used specifically to mean neoplasm. - When the term tumour is used non-specifically it can mean any swelling or proliferation of an organ or tissue. Some of these non-specific tumours could be neoplasms (Mawdesley-Thomas, 1971). Willis (1967) defined a tumour (in the specific sense) as "an abnormal mass of tissue, the growth of which exceeds and is uncoordinated with that of the normal tissue, and persists in the same excessive manner after cessation of the stimuli which evoked the change." "Neoplasm" refers to any new and abnormal growth, and "neoplasia" is the process of their formation (Mix, 1986). Mammalian neoplasms are classified as either malignant - characterised by rapid, invasive, unrestricted growth, or benign - slow-growing, non-invasive growth. In fish and shellfish pathology it is not always easy to differentiate benign and malignant growth.

A particular example of note is the term 'hepatoma', which is frequently used to designte tumours arising in the liver. This term has no precise histological meaning and should be discarded according to the International Histological Classification of Tumours (WHO, 1978).

Other words which are used in the non-specific sense include: nodule - a small node or lump, hyperplasia - a proliferation of cells (not synonymous with neoplasia); preneoplastic lesions - which may or may not develop into neoplasms, xenomas - tumours formed by parasites, but which are not neoplasms; and pseudotumours - xenomas, nodules or tumour-like growths. In higher animals, such an example would include the granulomas associated with tuberculosis (Bucke & Mawdesley-Thomas, 1974). Gross and cytological similarities between certain non-neoplastic conditions and neoplasms in fish have been critically reviewed (Harshbarger, 1984).

2. Neoplasia in marine shellfish

2.1 Introduction

In the marine environment, reports of cancerous type diseases are entirely related to proliferative disorders and neoplasms in the bivalve molluscs (Mix, 1986). Both proliferative disorders and neoplasms in this group of animals have stimulated controversy ever since the conditions were first described in the 1960s (Couch, 1969a; Farley, 1969a; Farley & Sparks, 1969).

2.2 Neoplasms occurring in bivalve molluscs in European Waters

Alderman et al. (1977) described abnormal haemocyte conditions affecting flat oysters, Ostrea edulis, in northern Spain and Yugoslavia. The authors recorded mortalities up to 35% in these studies, but they could not detect a pathogen and therefore hypothesised that local physical or chemical water conditions may have been implicated in the induction of the neoplastic conditions in oysters from these two widely-separated European sites. Balouet (1983, 1985) recorded a 1% prevalence rate of haemocyte neoplasms in O. edulis from coastal waters of Brittany, France. However, he found no evidence of abnormal mortalities in the oyster populations and considered the pathological problem may have been associated with spawning and/or abnormal stress. More recently, in France, Balouet et al. (1986) found an increase in haemocyte neoplasms in oysters, predominantly in the summer months. They paid particular attention to the areas affected by the AMOCO CADIZ oil spill but found no increase in the prevalence of oyster neoplasia between areas. Bucke & Feist (1985b) briefly mentioned occasional "minimal-to-marked" increases of haemocytes in O. edulis when they were surveying these animals for Bonamia ostreae infestations. They found no connection between haemocyte increases and Bonamia infections, but could give no reason for the former condition. Lowe & Moore (1978) identified haemocyte neoplasms in 3% of a population of mussels, Mytilus edulis, from a mussel bed in south-west England. Carcinogenic aromatic hydrocarbons had been detected in mussels from this bed, but the authors could not specifically correlate the disease conditions with the presence of the aromatic hydrocarbons. Following this report, Green & Alderman (1983) surveyed mussels from waters around the United Kingdom. Only occasional mussel neoplasms were identified. The authors' generalised statements suggested that neoplasia occurred in mussels but without specific correlation with either hydrocarbons or other pollutants, especially as some of the neoplastic mussels came from clean areas.

In Ireland, proliferative haemocyte disorders have been observed in 40% of a sample of common cockles, Cerastoderma edule, from Cork Harbour, (Twomey & Mulcahy, 1984), but there was no correlation with hydrocarbon contamination demonstrated. More recently, Poder & Auffret (1986) and Auffret & Poder (1986) described a 46% prevalence of cancerous lesions in cockles sampled from northern Brittany, France. The high prevalence of sarcoma in this species is of special interest, and even more revealing was the fact that the highest rate was not at Aber Wrac'h (site of the AMOCO CADIZ oil spill), but an area some distance away and therefore hydrocarbons were not considered to be responsible (Poder & Auffret, 1986).

Farley (1981) suggested that the neoplastic diseases exhibited by molluscs have a viral aetiology, based on his hypothesis that through the stages of phyletic development, the molluscs have developed a weak cellular defence system which is stimulated by oncogenic virus groups. At present, there is little evidence of a pollution-linked neoplastic condition in molluscs; evidence for such a link is only very tentative.

2.3 Neoplasms occurring in bivalve molluscs in North American waters

Outbreaks, or unusually high prevalences, of neoplastic disorders have been recorded in several populations of species of marine invertebrates in North America and around the Pacific Basin.

Oysters, clams, and mussels in certain regions have been the chief invertebrates found to suffer from presumed epizootic neoplastic diseases (Lauckner, 1983; Sparks, 1985; Couch & Harshbarger, 1985; Mix, 1986) (Table 1). The major neoplasm-type reported for these bivalve molluscs had been of presumed blood cell origin and has variously been called sarcoma, hematopoietic neoplasm, or blood-cell proliferative disorder. Suggested, possible causes have ranged from carcinogenic chemicals (Khudoley & Syrenko, 1978) to C-type retroviruses (Oprandy et al., 1981) to genetic disposition of individuals (Couch & Harshbarger, 1985). Prevalences have ranged from 1 per 5000 oysters examined to 8-12% of several hundred clams, oysters, or mussels. Recently, Farley et al. (1986) reported extremely high prevalences of blood-cell proliferative disorders in clams from Chesapeake Bay.

Bivalve molluscan neoplasms have been found in both contaminated and clean coastal waters (Lauckner, 1983; Couch & Harshbarger, 1985; Mix, 1986). Sites for outbreaks of molluscan neoplasms have been listed by Lauckner (1983) and Mix (1986) from North America, and other parts of the world.

Some recent evidence from laboratory studies does support chemical causes for certain experimentally induced molluscan neoplasms. Khudoley and Syrenko (1978) reported the induction of at least three neoplasm types in freshwater mussels with N-nitroso compounds. Couch et al. (1979) and Winstead & Couch, (1988) noted suspicious lesions induced in oysters exposed to both polycyclic aromatic hydrocarbons (PAH's) and diethylnitrosamine (DENA). Gardner et al. (1988) have reported that oysters experimentally exposed to heavily contaminated sediments from Black Rock Harbour, Connecticut, developed renal neoplasms. Though Khudoley & Syrenko (1978) observed the blood-cell form amongst their laboratory induced neoplasms, others have not been able to unequivocally produce blood-cell neoplasms by chemical induction in other bivalve molluscs. The aetiology of the blood-cell proliferative disorder in molluscs is therefore still unresolved.

3. Neoplasia in marine fish

3.1 Introduction

Mix (1986) critically reviewed over 500 publications on cancerous lesions in fish and shellfish which were considered by their various authors to be associated with environmental pollutants. However, Mix proposed that the only valid studies were to the long-term investigations on the effects of pollutants on fish and shellfish in Puget Sound, USA, by workers at the National Marine Fisheries Service (NMFS) Laboratory, Seattle, USA. Even then there were several deficiencies in the investigative procedures, such as a lack of data for age or sex of fish, sample sizes (especially from reference sites) were small, or there were no references to the outcome of the "preneoplastic" and "hyperplastic" lesions in fish (McCain et al., 1977, 1982; Pierce et al., 1978; Malins et al., 1980, 1982, 1983, 1984, 1987a,b). If the review of Mix (1986) is accepted as an authoritative assessment of most of the modern literature on cancerous lesions in fish and shellfish, it would appear noteworthy that there are few published reports in the European literature of any long-term studies on cancer in fish in relation to pollutants. Almost all of the reports of tumours in fish relate to either one-off or very short-term surveys. Where there are inferences of an association between the presence of pollutants and pathological conditions, they are largely conjecture based on circumstantial evidence.

3.2 Neoplasms occurring in fish in European Waters

Although the main interest in this report is focussed on marine fish, where appropriate data on freshwater fish exist these are also included.

3.2.1 Diverse neoplasms and "tumours"

Most of the data relating to tumours in fish and shellfish are referenced at the RTLA and the diagnostic interpretations are based on several expert opinions. Of the European accessions in this Registry, none refer to epizootics, but are classified by the histological characterisation, eg tumours of epithelial, haemopoietic, non-haemopoietic, mesenchymal tissues and special classes including pigment cell tumours, teratomas and tumours associated with the peripheral nervous system (Harshbarger et al., 1981). Many of the tumours described in fish from European waters are those associated with epithelial and non-haemopoietic mesenchymal tissues, ie connective tissues (Bucke & Feist, 1985a, 1986).

There have been several recordings of "tumours" associated with the pseudobranchial tissues of cod Gadus morhua and other gadioids, not only in the North Sea, but in the Northern Atlantic and Pacific Seas (Egidius et al., 1981; Watermann & Dethlefsen, 1982; Morrison et al., 1982). The cell types which make up these "tumorous" masses are atypical fish cells and have similarities to the X-cells' occurring in skin tumours in some North Atlantic flatfish species (Wellings et al., 1976) and even more surprising, similar cell types occur in the gills and other internal organs of North Sea dabs Limanda

limanda (McVicar et al., 1987). In the North Sea and the Barents Sea, the prevalence of the pseudobranchial "tumours" is less than 1% in a population sample (Egidius & Monstad, 1982; Watermann et al., 1982). To the inexperienced observer, these fleshy "tumours" could look like neoplasms and many scientists record them as such and have even associated them with pollution (Stich et al., 1976a). However, comprehensive studies of the X-cells (which make up these "tumours") including assessment of their biochemical profiles, clearly established them to be protistan parasites resembling a type of amoeba (Dawe, 1981). Furthermore, prevalence levels are a function of population densities of the susceptible gadoid species (Watermann et al., 1982).

The papillomatous syndrome in the European eel, Anguilla anguilla, is another example of a tumour where there is strong evidence for an infectious aetiology. These tumours are epidermal in origin, normally situated at the oral aperture, sometimes growing quite large and causing debilitation to the eel because it cannot feed properly (Peters & Peters, 1983). The epidemiology of papillomatosis in eels has been reviewed by Deys (1976) who was of the opinion that the condition primarily occurred in the Baltic Sea and over the past 50 years had spread to estuaries of rivers in the southern North Sea, thus following the pattern of natural infection in a population. Although a virus has been isolated and associated with the disease, it has not been unequivocally demonstrated to be the causal agent (Schwann-Pfizner, 1976; McAllister et al., 1977) and a multifactoral cause has been proposed, which includes pollution (Peters & Peters, 1983). Möller (1984) strongly disagreed that pollutants were part of the multifactoral cause, and he pointed to the reports of eel papillomatosis from relatively-uncontaminated waters in Scotland (Hussein & Mills, 1982).

Further examples of papillomas in fish from European waters, include the epidermal papilloma of dab (Johnstone, 1925). Prevalences of this condition vary considerably in dab populations in northern European coastal waters (Wootten et al., 1981; Dethlefsen, 1984; Bucke & Nicholson, 1987). There is a technical point which should be corrected about the dab papilloma: histological evidence shows that by far the greater incidence of lesions in individual fish are not papillomatous but are hyperplastic lesions (Bucke, 1988), and hyperplasias should not be classified by pathologists as neoplastic lesions (Willis, 1967). Therefore, when percentage prevalences are presented for papilloma in dab - up to 10% in some areas of the North Sea (Dethlefsen, 1984), the actual true prevalence of the benign papillomatous tumours could be less by a factor of 5 or 10. Peters & Watermann (1979) suggested hyperplasias are precursors of papillomas, but that hypothesis has not been proven.

Wolthaus (1984) noted that the epidermal hyperplasia/papilloma in dab was subject to considerable seasonal variation. In the freshwater environment such epizootics are not uncommon and have been reported by early biologists even as long ago as the 16th century (Gesner, 1563; cited by Mawdesley-Thomas & Bucke, 1967). Pollutants have not been seriously considered as a cause of epidermal papillomas in freshwater fish, but a viral aetiology has been proposed (Wolf, 1972; Bloch et al., 1986).

Lymphosarcoma of pike Esox lucius, is an interesting condition with a controversial aetiology, because, although it occurs over widely separated geographical areas, ie Scandinavia, Ireland and North America (Sonstegard, 1976), it has been strongly advocated to be associated with the presence of pollutants in the brackish coastal waters of the southern and central Baltic Sea (Ljungberg, 1976). Other workers tend to disagree that pollution is a causal factor because the disease has been demonstrated to be transmitted and frequently occurs in non-polluted waters (Mulcahy, 1976). At present there is more evidence for the suggested viral aetiology, because virus-like particles have been isolated from infected fish (Papas et al., 1977), and transmission has been achieved by intraperitoneal injection of cell-free material into uninfected pike (Mulcahy, 1976; Sonstegard, 1976).

In Europe, there have been several surveys for neoplasia in fish, in both freshwaters and river estuaries (Bucke, 1976; Köhler & Holzel, 1980; Kurelec et al., 1981; Slooff, 1983; Anders & Möller, 1985, Kranz & Peters, 1985; Peters et al., 1987). Bucke (1976) described adenocarcinoma of the thyroid occurring at 3% prevalence level in a population of roach Rutilus rutilus, inhabiting a lake in central England. Other fish present in this water included sticklebacks Gasterosteus aculeatus and tench Tinca tinca, but these species were not found to be affected. The water was contaminated by effluents from a nearby steel works (Solbé, 1973). However, because there were no follow up

studies, or related laboratory investigations, the correlation between neoplasia and environmental contamination was tentative. The cause could well have been attributed to iodine deficiency or a genetic disorder.

3.2.2 Hepatic neoplasms

If pollutants have a role in cancer induction in fish it is most likely that the neoplasms will occur in the liver. In research studies involving the exposure of fish to various carcinogens, where positive effects have been recorded, they have nearly always indicated some form of liver pathology, including certain stages resembling hepatic carcinogenicity (Scarpelli, 1975; Hendricks et al., 1984; Couch & Courtney, 1987).

In Europe, systematic studies on the effects of chemicals on fish livers have lagged behind those of North America, although there was considerable interest in the aflatoxin/hepatic neoplasia syndrome in rainbow trout in the 1960s (Wunder, 1973; Ghittino, 1976).

Kuralec et al. (1981) reported on an extensive survey in the polluted Sava River, Yugoslavia. They examined 200,000 fish, representing 21 species, for tumour frequency. The authors established that levels of mutagens both in water and fish were "raised", compared with samples from a control river. Macroscopical and histological results did not produce any evidence of tumours in liver or elsewhere. Slooff (1983) made a similar survey, this time examining 7,737 fish of 62 species from the River Rhine and its tributaries, and included an isolated lake as a control area. This study was in response to a previous study, in which mutagenic/carcinogenic agents in waters from the Rhine and its tributaries had been identified (Slooff & van Kreijl, 1982). Results from Slooff's (1983) survey revealed a total of 8 tumours, including 6 liver tumours in bream Abramis brama, and two thyroid tumours in roach. All tumours were found in fish from tributaries of the Rhine and not from the main river. The conclusion reached by the author was that carcinogenic substances in the Rhine tributaries were likely to be associated with these neoplasms (<0.1% prevalence). However, the substances were present in lower levels than reported in North American studies where higher prevalences of tumours in fish from contaminated waters have been reported (Black et al., 1980). Slooff (1983) suggested that the low incidence might have been due to roach and bream (the predominant species present) being less susceptible to developing neoplasms than certain other species of fish. It is worth noting that there is a report of earlier work which involved exposing rainbow trout over a long-term to Rhine River water, and in these studies liver tumours did not develop (Poels et al., 1980).

Köhler & Holzel (1980) examined livers and other tissues from flounder Platichthys flesus and smelt Osmerus eperlanus, sampled from the Elbe River estuary but did not identify tumours. Yet Anders & Möller (1985) recorded up to 8% prevalence of epidermal papilloma in the smelt from this same river and hypothesized that the causal agent was a Herpes virus possibly associated with hormonal stress. Kranz & Peters (1985), and Peters et al. (1987) examined livers from ruffe Gymnocephalus cernua, flounder and smelt, also in the Elbe River. These authors described several histopathological changes which they suggested were neoplastic nodules, although they did discuss the problem of whether the livers were regenerative centres, or even centres of heavy glycogen deposition. They pointed out that the nodules may not have been neoplastic because no "malignant tumours", ie liver carcinomas, were observed. It is a pity that they used the ambiguous term "neoplastic nodules", because it quickly became interpreted by the laity as "cancerous".

Falkmer et al. (1976) identified liver neoplasms in hagfish Myxine glutinosa, with higher prevalences in the polluted Gullmar Fjord, Sweden, than in the open sea (5.8% to 2.9%, respectively). These authors suggested PCBs were the cause of the neoplasms, but could not offer substantive facts, including chemical analysis, for this hypothesis. Therefore, these conclusions must be considered dubious (Mix, 1986).

Nounou et al. (1981) made a survey of fish species in French coastal waters. The authors described a number of histopathological lesions in various organs including pseudo-nodules in livers of cod Gadus morhua, and shad Alosa sp. None of these lesions were neoplastic, and the causes were considered to be associated with infectious or parasitic agents. However, the authors' supporting

evidence, that there might be an association with pollutants, must be considered tenuous. Haensley et al. (1982) examined livers from plaice Pleuronectes platessa, from an area of the north-west coast of France previously affected by the crude oil spill from the AMOCO CADIZ in 1978. No neoplasms were identified, although other histological changes were recorded, including liver changes, which the authors considered may have been related to the exposure to oil.

In the United Kingdom a number of studies have involved investigating marine fish for diseases and especially for the occurrence of neoplasia (Bucke et al., 1983a,b, 1984; Bucke & Feist, 1984, 1986). Bucke et al. (1984) examined 150 dab livers from fish, 25-38 cm length, sampled from the Dogger Bank area in the North Sea. 12% of those livers exhibited various nodular lesions. The histological characteristics of the hepatic nodules were non-encapsulated, but with distinct aggregates of either basophilic or eosinophilic hepatocytes. These cell-types were homogenous with small, centrally-placed nuclei. The overall size of the cells was smaller in the lesions than other surrounding hepatocytes, and often the suspect cells lacked cytoplasmic vacuolations, which are common in dab hepatocytes. It was uncertain whether those lesions were early stages of neoplasia. Further studies have revealed a number of idiopathic lesions in livers sampled extensively from populations of both North Sea and Irish Sea dabs (Bucke & Nicholson, 1987; Bucke & Stokes, 1988). These liver changes included non-specific necrotic lesions, megalocytic hepatosis, hepatocellular steatosis and foci of intracytoplasmic storage anomalies, clear cell foci and neoplasms. The neoplasms were diagnosed as liver cell adenoma following the definition proposed by Myers et al. (1987). Recent studies of the occurrence and pathogenisis of hepatic neoplasms in North Sea dab have shown the prevalence to be widespread but low (<5%). The neoplasms were confirmed positively by microscopical examination and other hepatic lesions considered to be possible pre-neoplastic stages were not included (Bucke et al., 1984). However, in studies which included all gross lesions on flatfish livers, including the smallest lesions from <1.5 mm upwards in size, the prevalence has been given as high as 40% (Vethaak 1986; 1987; Kranz & Dethlefsen, 1990). In both investigations it was concluded that liver neoplasms were considered to be the most relevant disease conditions that could be linked to pollutants, especially as higher prevalences were found in dab (and flounder Platichthys flesus from the more contaminated areas (Vethaak, 1986; 1987)), than from the less contaminated areas. As previously mentioned, Peters et al. (1987) described liver changes including nodular lesions from flounder and ruffe (Gymnocephalus cernua) samples from the Elbe River estuary. These authors gave histological descriptions of the nodular lesions and suggested they were precursors of hepatic neoplasms. However, the authors were cautious to point out that they were unsure that these pre-neoplastic lesions developed further because they had not found fish with well defined hepatic neoplasms. It appears that Peters et al. (1987) were describing similar histological changes to those reported by Bucke et al. (1984) and which were also observed in a further study (Bucke & Feist, in prep.).

3.3 Neoplasms occurring in fish in North American waters

3.3.1 Introduction

The incidence of neoplasms in bony fishes has been studied even more extensively than in invertebrates, as has their role as possible vectors of carcinogenic substances to higher trophic levels (Kraybill et al., 1977; Couch and Harshbarger, 1985; Mix, 1986; Masahito et al., 1988; Kimura, 1988; Hard et al., 1979).

Because of dramatic findings (occurrences) of hepatic lesions and bona fide hepatic neoplasms in several populations of marine fishes, considerable efforts in chemical surveys and tumor prevalence surveys (Table 2) have been made in estuarine or coastal regions of North America and Japan. In marine bony fishes, the liver is exposed to ingested substances via the alimentary tract and absorption pathways. Laboratory studies have demonstrated that hepatic cellular responses in fishes to carcinogen exposure is similar to that of many mammalian species (Couch & Courtney, 1987). Therefore, present field and laboratory evidence support the concept that certain hepatic conditions of feral fishes probably reflect the quality of their environments, particularly in terms of chemical exposures. In other words it is clear that certain hepatic lesions are a response to chemical exposure. Among these experimentally produced indicator lesions are hepatocellular carcinoma,

cholangiolar carcinoma, cholangiofibrosis (adenofibrosis), spongiosis hepatis, extreme fatty degeneration and necrosis and several other cellular and hepatic tissue injuries (see Couch, 1975; Couch & Courtney, 1987; Meyers & Hendricks, 1983; Hinton & Couch, 1980; and Möller & Anders, 1986). Several of these specific lesion types have been found also in livers of feral fish from populations from heavily chemically contaminated coastal waters such as areas of Puget Sound (Myers et al., 1987), Boston Harbor, Massachusetts (Murchelano & Wolke, 1985), the Hudson River estuary, New York (Smith et al., 1979), and Elizabeth River, Virginia (Vogelbein et al., 1990). Presently, the simplest explanation for the causes of these specific liver lesions is exposure to chemical pollutants. There is no present evidence that the above listed liver lesions are caused by natural, endogenous factors. Neoplasms of other tissues, found in the field tumour surveys and studies, are of uncertain aetiologies.

3.3.2 Kinds of Carcinogens Found in Marine Environments around North America

An important volume relating to distribution of carcinogenic substances in the marine environment was published by Malins and Jensen in 1988. This volume presents up-to-date reports on the status of marine pollutants and many of their effects, including carcinogenic responses in aquatic species. The reader is referred to this volume as a detailed review of chemical carcinogens in marine environments of North America, Pacific basin regions, as well as Europe.

Couch & Harshbarger (1985) stated that "fish liver metabolises indirect acting carcinogens through pathways creating reactive intermediates, and fish experimentally exposed to known carcinogens virtually always develop liver neoplasms".

Malins et al. (1982, 1984, 1988) from the US National Marine Fisheries Service (NMFS) have presented some of the most thorough chemical analytical data on carcinogens in their studies of areas of Puget Sound, Washington, USA. Most of their work focused on sites that yielded relatively high prevalences of bottom fishes with liver lesions, some of which were neoplasms. Many of the compounds found in sediments and fish were either directly or indirectly (following metabolic change) capable of reacting with DNA, and many compounds were known carcinogens (eg polycyclic aromatic hydrocarbons - PAH's). PAH's are widely distributed in coastal, estuarine, harbour, and sound waters around North America, and therefore have been one of the foremost suspect chemical groups as possible etiologic agents of fish neoplasms, particularly of lesions associated with liver or skin in bottom dwelling species (intimate, prolonged contact with sediments). Another west coast area studied and found contaminated with PAH's was San Pedro Bay near Los Angeles (Malins et al., 1987b). However, despite this intensive research effort the workers at the NMFS can only put forward "suggested evidence" that the observed liver lesions are associated with exposures of fish to toxic chemicals (Malins et al., 1987a).

Other North American marine sites that have been shown to have relatively high concentrations of PAH's include Boston Harbour (Zdanowicz et al., 1986), North Atlantic Coast, including Chesapeake Bay (O'Conner & Huggett, 1988; Huggett et al., 1987), several northern Gulf of Mexico sites (Kennicutt et al., 1988) and Elizabeth River, Virginia (Vogelbein et al., 1990).

Kimura (1988) reviewed the published findings of organic and metal-compound contamination along the coasts of Japan. He provides an excellent chronological annotation of specific chemical contaminants in Japanese waters and the effects on species that were associated with the contamination.

Apart from PAH's, and other suspect hydrocarbon compounds, the roles of many other reported chemical and metal contaminants in relation to possible causes of cancers in aquatic species is very uncertain; therefore, much more investigation of non-PAH compounds and agents is required to determine their roles in carcinogenic risks to biota.

Table 3 presents a list of chemicals, groups of chemicals, and industrial process products that are considered carcinogenic for humans (IARC, 1987). Few of these agents have been found in high concentrations in marine waters, sediments, or tissues in North America and Pacific Basins. In

Japan, and in North America, chromium and arsenic have been found in marine animals (Eisler, 1986, 1988a; Kimura, 1988; Friberg, 1988). However, it is of importance that neoplasms have been experimentally induced in fishes in the laboratory with other carcinogenic PAH's, eg B(a)P) (Couch & Harshbarger, 1985) and, further, that many of the constituent compounds of soots, tars, and mineral oils have also been found in marine sediments and waters and are probably, mainly, of anthropogenic origins.

The GESAMP list of harmful chemicals carried by ships contains a number of definite animal and suspect human carcinogens (GESAMP, 1989). Many of these agents (eg arsenic, creosote, chlordane, DDT, dieldrin, heptachlor, lindane, and PCB's) have been found in marine sediments, waters, and tissues (Malins & Jensen, 1988). However, our knowledge of their carcinogenic potential to marine species is limited, particularly when they are exposed to the chemicals in the marine environment rather than under laboratory conditions.

Table 4 is a partial list of chemical agents that have been laboratory tested for carcinogenicity in fishes. This table affords the reader an opportunity to examine the range of chemicals, fish species, and carcinogenic responses of fishes experimentally studied to date.

It is clear from experimental, laboratory studies that neoplastic responses of marine and freshwater fishes, to many chemical carcinogens, are similar to those of mammalian test species such as rodents (Couch & Courtney, 1987, Hinton et al., 1988; Masahito et al., 1988), and that feral fishes are victims of neoplastic diseases, some of which are probably caused by chemical contaminants in their environments (Myers et al., 1987; Kimura, 1988; Murchelano & Wolke, 1985). Therefore, it is probable that at least some of the neoplasms (particularly, hepatic cancers) found in feral fishes from contaminated waters are caused by chemical exposure. Further studies, including experimental exposures of fishes to contaminated sediments and water, should aid in confirming and clarifying this highly probable relationship.

4. Marine Fish and Shellfish - Carcinogens: Conclusions

The data available in Europe and North America regarding the effect of carcinogens in marine species differ somewhat in the strength of evidence for or against a causal association.

In Europe there have been no long-term studies to monitor the presence of neoplasms in fish or shellfish. Furthermore, there have not been any laboratory studies on neoplasia induction in species where neoplasms have been regularly identified, in order to find out whether these animals are particularly sensitive to even single chemicals let alone the complex mixtures of chemicals which are to be found in the environment. Perhaps not surprisingly therefore there is no unequivocal evidence that neoplasms in feral fish and shellfish in European waters are the result of exposure to contaminants. However, neoplasms are now being recorded in fish and shellfish, and without any proof, some workers are implying that they are the result of the effects of pollutants. Unfortunately in some cases the pathological terminologies used by the European workers are incorrect, and tumours other than neoplasms are sometimes included in overview reports, grossly exaggerating the real position.

In North America, scientists have made some progress in standardizing the histological definitions of liver tumours in fish, eg trout liver cancer (Halver & Mitchell, 1967; Hendricks et al., 1984). A book or Atlas is shortly to be published, edited by Dr C Dawe et al. which will provide an exhaustive description and nomenclature of fish neoplasms. The publication contains chapters, written by experts, on neoplasms derived from all tissues. Recently, the NMFS group has published a comprehensive resumé of hepatic neoplasms, putative preneoplastic lesions and other spontaneous lesions in a pleuronectid species (Parophrys vetulus) (Myers et al., 1987). The outcome of this study was that the hepatic lesions in the feral fish population were demonstrated to be morphological similar to hepatic lesions experimentally induced in rodents by certain hepatocarcinogens. Thus suggesting that Parophys vetulus may be a useful indicator for hepatocarcinogens in the aquatic environment. Furthermore, in a later report the NMFS group (Malins et al., 1988) emphasized that because of the complexities of polluted aquatic environments, understanding actual cause-and-effect relationships

between exposure of aquatic organisms to pollutants and disease necessitates the involvement of laboratory studies.

Prevalence of neoplasia in fish, or indeed shellfish (molluscs), is relatively low and none of the studies reported, even those where the terminology used is questionable, have suggested that populations, even at local level, are seriously threatened. The adverse effect on the individual fish is undisputed. Thus, whilst further work is necessary to establish the role of different chemicals and perhaps long-term trends in the numbers of individual organisms affected, at this point in time the existing restrictions on inputs of known carcinogens seem to be of a sufficiently precautionary nature to prevent serious problems arising among marine species.

So far as further investigations with marine species are concerned it is worth noting that mammalian pathologists have taken many years of inter-laboratory collaboration and discussions at seminars and conferences in order to agree on the classification of liver tumours in rats and mice, respectively (Squire & Levitt, 1975; Frith & Ward, 1980). Fish pathologists have benefitted from these arguments concerning mammalian tumour classifications and, in principle, have been able to apply many of the same questions and answers to fish. However, even in rats and mice, species which are used extensively in cancer research, there are still questions concerning the significance of the neoplastic nodules (eg adenoma) (which are similar to those described in fish) (Anon, 1986). There can be little doubt that the story would be clarified considerably if all pathologists working in the field of fish and shellfish neoplasms were to:

1. Collaborate in seeking second opinions and standardisation of reporting.
2. Exchange examples of fish neoplasms between laboratories.
3. Establish registries for collections of neoplastic conditions.
4. Use the Registry of Tumours of Lower Animals, Smithsonian Institution, Washington DC, USA as a central reference point.
5. Use molecular genetic techniques to identify malignant cells.

B. ASSESSMENT OF CANCER RISK ASSOCIATED WITH CONSUMPTION OF SEAFOOD

1. Introduction

Marine animals with conspicuous neoplasms or tumours are usually discarded before human consumption. In the unlikely event that a fish or invertebrate with a neoplastic disorder were eaten, there would probably be little risk of transmission of the disease to the consumer because neoplasms are not known to be transmitted in any animal group via consumption of neoplastic tissues. Therefore, the chief concern is exposure of humans to carcinogenic chemical agents present in marine food organisms.

The uptake and accumulation by marine organisms of organics, and metals, including potential carcinogens have been studied extensively (see reviews by McCain et al., 1988; Kennicutt et al., 1988; O'Connor & Huggett, 1988; Swain, 1988; Friberg, 1988). However, few studies have been conducted on the potential transfer of accumulated body burdens of chemicals to mammalian or, particularly, human consumers (Swain, 1988; Friberg, 1988; McKenzie-Parnell et al., 1988). Nonetheless human health studies of Minamata disease in Japan have shown that contamination of seafood with methyl mercury from an industrial source can be a cause of severe human diseases (Kimura, 1988).

Thus it is known that marine organisms can accumulate certain potential carcinogens and that clearly measurable concentrations of such chemicals are present in certain edible marine species (arsenic, PAH's etc) (Eisler, 1987, 1988a; Malins & Jensen, 1988). It is also clear that species with high fat reserves can accumulate relatively high concentrations of PAH's and other suspect organic compounds (Eisler, 1985, 1986, 1987, 1988b; McKenzie Parnell et al., 1988). Equally it is known that marine foodstuffs are not the only route of exposure of the human population and any overall risk assessment must take this into account.

2. Cancer Risk Assessment Methods

2.1 Hazard Identification

The only direct method of identification of a carcinogenic hazard in a human population is epidemiology and in some cases this provides strong evidence that a particular agent causes cancer under observed conditions of exposure. However in many other cases, because of unquantified and mixed exposure, ill-defined exposure populations and life-style factors, it is unclear whether there is a causal relationship between exposure to a particular agent and the incidence of cancer. Even where there is clear evidence of a causal relationship in a human population there is reason to doubt whether humans exposed to much lower amounts or by different routes of exposure are at risk (Houk, 1989; Rugen et al., 1989).

Long-term animal studies provide a controlled method to identify carcinogenic potential and by far the largest number of carcinogens have been discovered by this method. However, interpretation of animal results in terms of human hazard depends on a number of factors (WHO, 1987).

Both in vivo and in vitro short-term tests facilitate the understanding of the mechanisms by which the longer-term effects could have been caused and thereby enable their practical significance to be assessed. While hazard identification is essentially qualitative its use in assessing the likelihood of carcinogenic effects in humans has been evaluated in a number of ways. One of these is the IARC classification which, in the absence of positive epidemiology data, rates the probability of effects in humans mainly according to the weight of evidence of carcinogenicity in animal studies by any dose-route (IARC, 1987). Other methods (WHO, 1987) take account of the probable mechanism of the carcinogenic response; whether the dose routes used are likely to be relevant to human exposures; whether the response is an increase in the incidence of spontaneously occurring tumours or the production of rarer tumours; whether there is a dose-response relationship in the production

of tumours; whether a difference in metabolism between experimental animals and man is likely to indicate a difference in carcinogenic response.

2.2 Assessment of human exposure

In considering the possible effects of consuming seafood it is necessary to characterise the communities and individuals according to the amounts they consume. Although there are likely to be large differences between communities in different parts of the world in their consumption of seafood and between those who eat vertebrate fish or shellfish, for simplicity the consumption figures used previously by GESAMP (Friberg, 1988) will be used here. These indicate that the world average fish consumption is about 16 g/day and that the 97.5 percentile is about three times the average - a figure which is in general accord with that of Coomes et al. (1982), in distinguishing between normal and "extreme" food consumption. Friberg states that, in some countries 60 g/day fish consumption is more representative and he considers the case of population groups consuming 150 g/day. Such figures compare reasonably well with WHO assessments. For example based on FAO food balance data, the European regional average consumption of seafood (fish and shellfish) is 60 g/person/day and in East Asia 79 g/person/day. 150 g/day is the figure used to represent high consumption for the purpose of this report.

Some other assessments of risk to seafood consumers, however, assume the existence of certain groups consuming more than 150 grams/day seafood. The possibility that these groups exist and that they involve the consumption of highly contaminated seafoods cannot be ruled out.

For each level of seafood consumption, the carcinogenic risk from marine pollutants will vary according to the concentration present, which will vary from place to place and from time to time. In the present assessment it is assumed that relatively high levels of seafood consumption coincide with high levels of contamination. Such an assessment of carcinogenic risk is likely to be conservative for most consumers of fish and shellfish.

The acceptable daily intake (ADI) is the daily dosage of a chemical which, during an entire lifetime, appears to be without appreciable risk on the basis of all the facts known at the time. "Without appreciable risk" is taken to mean the practical certainty that injury will not result even after a lifetime of exposure. The acceptable daily intake is expressed in milligrams of the chemical, as it appears in the food, per kilogram of body weight (WHO, 1990a).

Where an ADI has been established for a particular pollutant it will be noted whether the intake from seafood is likely to be a substantial part of the ADI. A judgement will then have to be made whether or not the carcinogenic risk from eating seafood is likely to be significant with respect to consumption of other foods. ADIs are arrived at by taking into account the toxicological, pharmacological and chemical data of a specific substance. Where the substance is present in the environment, the amount ingested through environmental sources is taken into account in estimating the ADI. Particular attention is paid to a "no-observed-effect-level" (NOEL) in those considerations; the risk that may be incurred by especially susceptible groups, such as children and old people is also taken into account.

The ADIs referred to in this report have been estimated by committees of experts from international bodies (FAO and WHO) and are made available to the public in reports from these committees.

The following extract from WHO (1987) provides an example of how the Joint FAO/WHO Expert Committee on Food Additives (JECFA) approaches the setting of an ADI:

"JECFA generally sets the ADI of a food additive on the basis of the highest no-observed-effect level in animal studies. In calculating the ADI, a "safety factor" is applied to the no-observed-effect-level to provide a conservative margin of safety on account of the inherent uncertainties in extrapolating animal toxicity data to potential effects in the human being and for variation within the human species. When results from two or more animal studies are available, the ADI is based on the most sensitive

animal species, i.e., the species that displayed the toxic effect at the lowest dose, unless metabolic or pharmacokinetic data are available establishing that the test in the other species is more appropriate for man.

Generally, the ADI is established on the basis of toxicological information and provides a useful assessment of safety without the need for data on intended or actual use and consumption. However, in setting ADIs, an attempt is made to take account of special subpopulations that may be exposed. Therefore, general information about exposure patterns should be known at the time of the safety assessment. For example, if a food additive is to be used in infant formulae the safety assessment is not complete without looking carefully at safety studies involving exposure to very young animals".

In cases where JECFA considered that a provisional tolerable weekly intake (PTWI) was a more appropriate concept than an ADI, PTWI has been considered in the context of exposure to a particular material from seafood.

An alternative, and more conservative, approach, is to assume no threshold of effect exists and to calculate the level of exposure over a life-time which would just give rise to an acceptable risk of causing cancer within that life-time. For most of the substances considered in this review this approach was not considered necessary as internationally acceptable ADIs have been set and this process is based on the belief that a no effect intake level does exist. To avoid the use of two different approaches, the threshold approach was adopted for all substances considered in this document for which, in most instances, either acceptable daily intakes (ADIs), provisional tolerable weekly intakes (PTWIs), or similar health protection criteria, are available.

2.3 Dose-response assessment

Because long-term animal studies are carried out at very high exposure levels and human exposure is generally very low, the animal data must be evaluated to indicate possible effects at low exposures. Many mathematical models have been used for this low-dose extrapolation, giving risk estimates which vary enormously (Somers, 1984). As suggested by a number of workers (Park, 1989), the model chosen should be appropriate to the type of carcinogenic mechanism.

The carcinogenic mechanism most discussed is one where the carcinogen or one of its metabolites reacts with DNA. For these genotoxic carcinogens it is theoretically possible to extrapolate to low doses by measuring carcinogen - DNA adducts at different dose levels. However, this theory applies to the effective dose (the dose at the target organ) and not necessarily to the administered dose. Hoel et al., (1983) point out that administered dose is not proportional to the effective dose where kinetics of the transport or the metabolism of the carcinogen is saturated in the study under consideration. This will usually be the case in the majority of animal carcinogenicity studies which are carried out at or about the maximum tolerated dose. It is therefore desirable that efforts be made to identify accurately the effective dose, since this will permit better elucidation of the dose-response curve, determination of the NOEL and better extrapolation to man.

For non-genotoxic carcinogens a non-malignant pathological change which precedes the appearance of malignant tumours has been described for a number of carcinogens. Butterworth (1989) suggests that this type of carcinogenic mechanism can be identified by the pathological changes and appropriate extrapolation models can be chosen. It has been argued (Clayson et al., 1989) that, where there is a threshold dose below which the non-malignant pathological change is not observed, the most appropriate method of establishing a safe dose for humans is to apply a safety factor to that "no effect level".

2.4 Risk Assessment

This process integrates hazard identification, exposure assessment and dose-response assessment. Accordingly this review makes a semi-quantitative assessment of the carcinogenic risk to humans by:

(a) Weighting the evidence for each pollutant according to whether the effect is likely to be relevant to a seafood-consuming population.

(b) By estimating the exposure to each seafood pollutant in the context of its occurrence in other foods and water and assessing whether effects observed at high exposure levels are likely to be predictive of effects at more relevant exposure levels.

3. Metals and Metalloids found in seafood

3.1 Arsenic

Friberg (1988) concluded that high consumption of seafood (150 g/day) could result in an intake of inorganic arsenic which could increase the risk of skin cancer to an extent which is not negligible. However, this conclusion assumes that a substantial proportion of arsenic in seafood is inorganic and, as far as can be established, this is not the case.

The evidence that inorganic arsenic in drinking water causes an increase in skin cancer in human populations over-rides any evidence from inhalation exposure in humans or from animal studies. However, the inorganic arsenic content of drinking water which is associated with incidence of skin cancer (Cebrian et al., 1983 and WHO, 1981) represents a daily intake about an order of magnitude greater than that estimated from extreme consumption of seafood.

The recent meeting of JECFA (WHO, 1989a) confirmed a previously assigned provisional tolerable weekly intake (PTWI) of 0.015 mg/kg bodyweight for inorganic arsenic with the clear understanding that the margin between the PTWI and intakes reported to have toxic effects in epidemiological studies was narrow. JECFA further concluded that human exposure to levels of inorganic arsenic below those which cause arsenism do not appear to carry a carcinogenic risk. As for intakes of organic arsenic compounds from the fish component of the diet, these do not appear to be a cause for concern (WHO, 1989a).

Moreover, application of this PTWI to the data given by Friberg (1988) is fairly reassuring. This shows that the PTWI for inorganic arsenic would not be reached at high concentration of arsenic in seafood (10 µg total As/g), even by consumption of 150 g seafood/day, 7 days/week by a 60 kg person, assuming that 5% of the total arsenic is present in the inorganic form.

IARC (1987) evaluated arsenic and concluded that inorganic arsenic is carcinogenic to humans, but there are no adequate data on the carcinogenicity of organic arsenicals. A similar conclusion was reached by JECFA (WHO, 1989a). There is therefore no indication that organic arsenic compounds in seafood are carcinogenic.

3.2 Cadmium

Friberg (1988) concluded that it was possible that long-term ingestion of shellfish could increase the cadmium concentration in the human kidney and that it was possible to identify groups of people at increased risk.

The carcinogenicity of cadmium is discussed in WHO (1989a) and it is clear from this that in experimental animals the metal and its salts give injection-site tumours after subcutaneous or intramuscular injection; Leydig cell tumours after single large subcutaneous doses and lung tumours after inhalation of aerosols. One study appeared to show an increase in prostate and lung tumours in workers occupationally exposed to cadmium but later studies failed to show good evidence of a causal association between industrial exposure to cadmium and incidence of prostate or lung cancer. From this evidence IARC (1987) concluded that cadmium and its compounds are probably carcinogenic to humans with "sufficient evidence of carcinogenicity in experimental animals and limited evidence of carcinogenicity in humans".

However, studies in which cadmium compounds are given orally do not indicate a carcinogenic response. A study in which cadmium was given to rats in drinking water at 5 mg/l for 2 years was negative for carcinogenicity, although the conditions of the study were considered to be inadequate by modern standards (WHO, 1989a). When rats were fed diets containing up to 50 ppm cadmium chloride for two years there was no increase in the incidence of tumours (Loser, 1980).

Leydig cell tumours are rare in humans and are not associated with exposure to cadmium (Ryan et al., 1982). On the other hand these benign tumours are common in rats of all strains and may be induced by hormonal disturbance (Mostofi & Bresler, 1976). They are therefore not reliable indicators of chemical carcinogenesis.

If there had been a causal association between occupational exposure to cadmium and carcinoma of the prostate, which according to Doll (1985) there probably was not, a similar causal relationship has not been found with dietary intake of cadmium. Among the countries with the highest dietary exposure to cadmium, Japan has one of the lowest incidences of prostate cancer. On the other hand Sweden, with among the lowest average dietary cadmium has among the highest rates of prostate cancer (Ryan et al., 1982).

Molluscs and crustacea appear to bioconcentrate cadmium to a much greater extent than vertebrate fish (Ryan et al., 1982 and Magos, 1989). In shellfish the cadmium appears to be protein-bound and not well absorbed from the human alimentary tract. Newton et al. (1984) found that in seven male volunteers eating brown crabmeat, only 2.7% of the cadmium was absorbed on average. In another group of people, consumption of oysters containing 5 mg/kg cadmium did not markedly increase the concentration of cadmium in the urine, although it did increase the faecal excretion of cadmium. However, in the non-smokers of this group an increase in blood cadmium was detectable after oyster-eating (Sharma et al., 1983).

In assessing the possible carcinogenic risk of eating seafood Friberg (1988) considers shellfish with cadmium concentrations "exceeding 1 mg/kg fresh weight". Magos (1989) gives the median concentration in molluscs as 1.6 mg/kg, brown crab meat as 14.4 mg/kg and lobster liver 12 mg/kg cadmium. Some recent publications (Luis et al., 1989; Gutenmann et al., 1988; Peerzada & Dickinson, 1988) give comparable concentrations of cadmium in shellfish while others (Gil et al., 1988; Hutagalung, 1989) give mean concentrations up to 5 mg/kg cadmium in molluscs and bivalves. Uthe et al. (1987) describe a situation in which a lobster fishery had to be restricted because of cadmium contamination from a nearby lead smelter. Before the source of cadmium was controlled, mean values up to 160 mg/kg cadmium were found in the digestive gland of the lobsters, with values around 0.8 mg/kg for the cooked meat of the claws and tail.

The kidney has been identified as the critical organ in relation to chronic exposure to relatively low levels of cadmium and in particular the renal cortex. The first adverse functional change is usually a low molecular weight (LMW) proteinuria, and intakes in the range of 140-255 µg/day have been associated with increased LMW proteinuria in the elderly. LMW proteinuria is not accompanied by any specific histological changes. In order that levels of cadmium do not reach critical concentrations in the renal cortex, JECFA recommended that total cadmium intake should not exceed about 1 µg/kg body weight/day continuously for 50 years. On this basis, the PTWI for cadmium was set at 7 µg/kg bw. Since the PTWI is derived from estimated accumulation of cadmium over a period of 50 years at an exposure rate equivalent to 1 µg/kg bw/day for adults, excursions above this figure may be tolerated provided that they are not sustained for a long period of time and do not produce a significant increase in integrated lifetime dose (WHO, 1989a). This PTWI, which is very conservative from the point of view of any possible carcinogenic effect, would be exceeded by the maximum rate of seafood consumption assumed in this review, especially if it included a high proportion of the brown meat of crabs or the digestive gland of lobsters. However, in view of the evidence that orally ingested cadmium is not carcinogenic and that tumours produced by other dose routes are not relevant to oral intake, there is probably no significant cancer risk from cadmium generally found in seafood. This conclusion probably holds even for situations in which there are high levels of cadmium in the food species, but these situations are cause for concern because of the other adverse effects of cadmium ingestion.

3.3 Lead

The assessment by Friberg (1988) states briefly that consumption of lead from seafood does not generally constitute a toxicological problem.

IARC (1987) evaluated the carcinogenicity of lead and lead compounds. Organolead compounds could not be classified as to their carcinogenicity to humans. Lead and inorganic lead compounds may possibly be carcinogenic to humans, with sufficient evidence of carcinogenicity in animals and inadequate evidence of carcinogenicity in humans.

The evidence for the carcinogenicity of lead is discussed by Schlag (1987) and consists mainly of studies in which rats showed a dose-related increase in kidney tumours when fed diets containing 500 mg/kg or more of lead acetate. A group of 250 rats fed 100 mg/kg of lead acetate (equivalent to 5 mg lead acetate/kg body weight/day or 3.2 mg Pb/kg body weight/day) did not have any kidney tumours and it appeared that the incidence of tumours depended on accumulation of lead in the kidney. Schlag also discussed some epidemiological studies which are suggestive of an association between occupational exposure to lead and a number of types of malignancy mainly of the digestive and respiratory organs. However, in these studies there was often exposure to other metals and attempts to find a quantitative relationship between lead exposure and cancer were not successful. There was a case in which a high concentration of lead was found in a renal tumour of an individual with a history of high lead exposure. This tumour was reported to show histological similarities with the kidney tumours in the lead-exposed rats.

Lead is ubiquitous in the environment and it is accumulated particularly by filter-feeding bivalves. Magos (1989) gives values up to 95 mg/kg for mussels near an industrial discharge but states that most values are below 3 mg/kg and around 0.025 mg/kg when "ultraclean" conditions of sampling and analysis are used. This tends to confirm that acceptance of analytical results for lead should depend on the quality of the methods used because of the probability of external contamination of the samples. Magos indicates that the lead content of vertebrate fish is an order of magnitude less than that of shellfish.

Later publications (Luis et al., 1989; Gutenmann et al., 1988; Marcus & Thompson, 1986) indicate lead contamination of shellfish at 2 mg/kg or less. However, Ober et al. (1987a) give results up to 6 mg/kg lead (converted to fresh weight bases). Falandysz (1985) gives results for flatfish in the Southern Baltic of 0.2 mg/kg lead or less confirming that vertebrate fish are generally less liable than shellfish to accumulate lead.

Compliance with the FAO/WHO PTWI for adults of 50 µg/kg bodyweight or 7 µg/kg bodyweight per day lead intake, may clearly not be possible for people depending for food on shellfish from highly contaminated areas. This PTWI has been established on the basis of specific toxic effects of lead and not on its carcinogenic properties. The toxic effects are primarily related to the haematophoietic system, the nervous system and the kidneys. The PTWI is based on the maximum intake from all sources that would not result in accumulation of lead in the body as measured by blood lead levels.

To assess the possible cancer risk from the lead content of seafood it is assumed that a 60 kg person consumes 150 g/day of shellfish containing 5 mg/kg lead; this would constitute a personal intake of 0.0125 mg/kg bodyweight per day of lead. The no-effect level for kidney cancer in the rat is 3.2 mg lead/kg bodyweight per day. The rat renal cancer appears to be mediated through massive kidney accumulation of lead, therefore human intake of lead in seafood would not constitute a significant cancer risk. There are two grounds for such a view; first it is questionable whether lead induced kidney tumours in rats is an appropriate carcinogenicity model and second, even if it is, the dose level causing kidney tumours in rats was much higher than that estimated via human intake from seafood.

3.4 Mercury

The predominant form of this metal in seafood is methylmercury, the significance of which as a food contaminant has been recently reviewed (WHO, 1989a; Tollefson & Cordle, 1986). These reviews

have been concerned with the neurotoxicological effects of methylmercury to a much greater extent than its possible carcinogenicity. Mitsumori et al. (1981) reported that methylmercury chloride (MMC), when given at not far from lethal doses, was a renal carcinogen in male mice. All animals given 30 mg/kg MMC in their diet died from neurotoxicity within 6 months and ten out of fifty-nine of those exposed to 10 mg/kg developed renal adenocarcinomas. No renal tumours were seen in control male and female mice, in male mice exposed to 0.4 or 2 mg/kg concentrations and in the female mice in any dose group.

A study of rats by the same investigators using the same dietary concentrations of MMC produced some nephrotoxicity but no increase in renal tumours (Mitsumori et al., 1984). Thus the weight of experimental evidence for the carcinogenicity of methylmercury is limited, because only one tissue site was affected, no clear-cut dose response relationship was observed and, only one species responded with cancer and within this species only one sex was affected.

A number of epidemiological studies (WHO, 1989a) describe neurotoxicity and renal tubular dysfunction in people exposed to methylmercury but no suggested association between this exposure and the incidence of cancer was found.

Humans exposed to methylmercury from contaminated fish show a significant relationship between the frequency of cells with chromosome aberrations and blood mercury levels (Skerfving et al., 1974). IARC (1989) has not evaluated the carcinogenic risks to humans of either mercury or mercury compounds.

JECFA established a provisional tolerable weekly intake of 200 µg (3.3 µg/kg bw) methylmercury for the general population and noted that the nervous system is the principal target tissue of methylmercury in humans. Recent neurotoxicity studies demonstrated a no-observed-effect-level of 10 µg/kg bw/day in the most sensitive animal species, in this case the rat (WHO, 1989a).

In addition to the data by Friberg (1988), information on the mercury content of seafood is given by May et al., 1986; Hamid & Embong, 1987; Gutenmann et al., 1988; Luis et al., 1989 and Hutagalung, 1989. These indicate that total mercury levels in shellfish vary from "not detectable" to 800 µg/kg (Ober et al., 1987a). Shellfish appear to be able to concentrate mercury direct from seawater and the levels probably depend on local sources of contamination. On the other hand the levels in vertebrate fish correlate to some extent with their position in the food chain - the large predators having the highest levels.

In shellfish methylmercury concentrations vary from 44-80% of the total mercury content, but in vertebrates are generally greater than 90% and do not vary appreciably across species (May et al., 1986). Fish is generally the largest source of mercury in the human diet (Coomes et al., 1982; Buchet & Lauwerys, 1983; Mykkanen et al., 1986).

The PTWI, established by WHO (1989a) of 200 micrograms of methylmercury (3.3 µg/kg bodyweight per week) for the general population, would be exceeded by a person eating three large meals per week of fish containing 500 µg/kg of methylmercury - a concentration which occurs in cod, for instance according to Friberg (1988) and which is just at the limit of several national limits for methylmercury in fish.

Assuming a 60 kg person consuming 150 g/day of fish containing 500 µg/kg methylmercury, this would result in a personal intake of 1.25 µg/kg bodyweight per day. The no-effect level for kidney cancer in the mouse is about 250 µg/kg bodyweight per day. Thus, such consumption is unlikely to constitute a significant cancer risk since the appearance of kidney cancer in one sex of one species (mice) suggests a non-genotoxic mechanism. Furthermore, there appears to be no evidence of increased cancer mortality in Japanese people who were poisoned by high concentrations of MMC in fish. The evidence for the genotoxicity of methylmercury (Fan, 1987) and chromosome aberrations in people eating fish appear to be equivocal and it is most likely that the kidney cancer in mice has an epigenetic mechanism. In this case the relatively high fish consumption considered would not constitute a significant cancer risk.

3.5 Nickel

Some nickel compounds are carcinogenic in humans and animals after inhalation exposure (IARC, 1987). Local tumours have also been produced in experimental animals after subcutaneous and intramuscular injections. However, oral exposure of mice and rats to 5 mg nickel/litre in the drinking-water did not produce a significantly higher incidence of tumours compared with controls. Addition of nickel sulfate hexahydrate fines (22.3% nickel) to the diet of rats for 2 years, at concentrations of 0, 100, 1000 or 2500 mg nickel/kg did not produce any carcinogenic response (WHO, in press).

Magos (1989) gives a mean of less than 5 mg/kg of nickel in seafood, based on a limited amount of data, although bivalves from two highly contaminated locations contained up to 34 mg/kg of nickel. Other data indicated nickel contents of 2.5 mg/kg or less in shellfish (Marcus & Thompson, 1986; Ober et al., 1987a) and 1.7 mg/kg or less in vertebrate fish (Falandysz, 1985; Denton & Bordon-Jones, 1986; Kasprzak, 1987).

Kasprzak states that the average daily human ingestion of nickel from food and water is 0.4 mg and his data indicate that intake from seafood is probably not a major part of this intake. Therefore, although the relative hazard probably depends on the form of nickel in the various foods, it is noteworthy that even comparatively high consumption of seafood would generally not result in a nickel intake appreciably greater than the average.

Since in animal experiments oral ingestion of nickel compounds did not produce cancer and epidemiological studies indicate that nickel dust in air increased only the incidences of nasal and pulmonary cancers, it seems unlikely that nickel in fish or shellfish presents any carcinogenic risk to consumers.

4. Organochlorines

Much of the data on the organochlorine contamination of seafood is more than a decade old and there is some evidence that, in spite of the persistent character of some of these compounds, particularly the older agricultural pesticides, environmental concentrations have fallen in more recent times (Skare et al., 1985; Huschenbeth, 1986).

4.1 DDT

DDT and its metabolites are some of the most frequently reported organochlorine contaminants in the environment. They are accumulated in aquatic organisms directly from water as well as from food (WHO, 1989b).

DDT fed in the diet has been found to cause liver tumours in mice and, to a lesser extent in rats. The lowest dose which caused these tumours in male, but not female, mice was 0.3 mg/kg bodyweight per day (WHO, 1979). The metabolites DDE and DDD also produced liver tumours in mice but at much higher dosages. The tumours were preceded by liver enlargement, an increase in endoplasmic reticulum and in microsomal enzyme activity. These changes are produced by a number of other compounds, including phenobarbitone, which also produce liver tumours in rodents. The changes and the tumours appear to be peculiar to rodents and the Joint Meeting on Pesticide Residues (JMPR) concluded that there is no significant risk of DDT producing tumours in humans (FAO/WHO, 1985).

Careful investigation of workers who had been occupationally exposed to DDT for as long as 25 years, did not reveal any evidence that DDT causes cancer in man. However, it was recognised that the number of workers was too small to detect a possible low incidence of cancer (WHO, 1979). DDT was negative for mutagenicity in the Ames test and in a dominant lethal assay. On the basis of these data and an overall no-effect level for toxicity of DDT of 0.25 mg/kg bodyweight/day in humans, an ADI of 0.02 mg/kg bodyweight was set by the JMPR in 1984 (FAO/WHO, 1985).

A survey of reports about vertebrate fish from widely different parts of the world (Magos, 1989; Gutenmann et al., 1988; Douabul et al., 1987; Ober et al., 1987b; Villeneuve et al., 1987; Falandysz, 1986; Huschenbeth, 1986; Skare et al., 1985; El-Dib & Badawy, 1985; Stout, 1980) indicates that the concentration of unmetabolized DDT in muscle tissue is, in many cases, below the level of detection (Villeneuve et al., 1987) but may average about 50 µg/kg in heavily contaminated regions (Falandysz, 1986). The sum of DDT and its metabolites has been reported to be as high as 5000 µg/kg (eg Huschenbeth, 1986). The concentrations in fish liver and liver oil are generally about ten times those in muscle, the highest value found being 7000 µg/kg (Magos, 1989). Most concentrations of DDT products in shellfish appear to be below 100 µg/kg but Magos (1989) gives an upper value of 800 µg/kg.

There is inadequate evidence for the carcinogenicity of DDT to humans but there is sufficient evidence of its carcinogenicity to experimental animals (IARC, 1987) although it appears the effect is peculiar to rodents. Thus, if a 60 kg person consumed 150 g/day of fish containing 50 µg/kg of DDT and its metabolites the daily intake would be 0.125 µg/kg bodyweight. This would constitute $^{1}/_{160}$ of the ADI and $^{1}/_{2400}$ of the lowest dose of unmetabolized DDT which caused liver tumours in male mice of the most sensitive strain tested. A daily intake of this scale would not involve any human cancer risk. Consumption of fish from more heavily contaminated areas would be undesirable because of the biological persistence of DDT but it is doubtful whether such exposure would involve a cancer risk.

4.2 Aldrin and dieldrin

These two insecticides are generally considered together because aldrin is readily converted to dieldrin so that it is the latter which is generally found in food.

Carcinogenicity studies on aldrin have been negative or equivocal but dieldrin has caused liver tumours when fed in the diet to mice. Studies in rats have not given significant evidence of carcinogenicity with either compound. The lowest dietary concentration which caused liver tumours in mice was 0.1 mg/kg dieldrin - equivalent to 0.015 mg/kg bodyweight (IARC, 1974). In a recent evaluation of the carcinogenicity of aldrin and dieldrin, IARC concluded that there was inadequate evidence for their carcinogenicity to humans and only limited evidence for the carcinogenicity to animals (IARC, 1987). Although there have been some equivocal results in different test systems, mutagenicity studies on aldrin and dieldrin have been essentially negative by the standard bacterial assays (Ashwood-Smith, 1981). The JMPR also concluded that aldrin and dieldrin are not carcinogenic. On the basis of levels causing no toxicological effects of 0.025 mg/kg body weight/day in rats and dogs, an ADI for aldrin plus dieldrin of 0.0001 mg/kg bodyweight was established by the JMPR (FAO/WHO, 1978).

A survey of reports (Magos, 1989; Douabul et al., 1987; Ober et al., 1987; Huschenbeth, 1986; El-Dib and Badawy, 1985; Kruse and Krueger, 1981; Stout 1980) indicates that the typical range of concentrations of aldrin plus dieldrin in the edible tissues of vertebrate fish is up to 150 µg/kg, apart from fish caught in the coastal waters of Chile in 1985 where one species contained 3000 µg/kg dieldrin plus 120 µg/kg aldrin (Ober et al., 1987b). The range in shellfish is up to 30 µg/kg except for a value of 462 µg/kg dieldrin given by Magos (1989).

As with DDT the main consideration in assessing the cancer risk from aldrin and dieldrin in seafood is that their carcinogenic activity appears to be typical of other microsomal enzyme inducers such as phenobarbitone, and peculiar to rodents particularly mice. Ribbens (1985) concluded from a limited epidemiological study of occupationally-exposed workers that there was no indication of specific carcinogenic activity of aldrin or dieldrin.

It would be very difficult for a person eating seafood from a contaminated region to avoid exceeding the ADI. Indeed, if a 60 kg person ate 150 g per day of fish containing 50 µg/kg aldrin plus dieldrin this would amount to slightly more than the ADI. However, the large safety factors generally involved in establishing an ADI provide assurance that exposure slightly exceeding the ADI is unlikely to result in any deleterious effects upon health (WHO, 1990a). Moreover, because of the lack of any evidence

of carcinogenic activity in occupationally exposed workers it seems very unlikely that such intakes would constitute a carcinogenic risk.

4.3 Heptachlor

This insecticide is readily metabolized to the more stable heptachlor epoxide and a mixture of these materials is found in foodstuffs.

A number of long-term animal studies has led to the conclusion that heptachlor is not carcinogenic in the rat and that the carcinogenic response in certain strains of mice is confined to the liver. A no-effect level for this liver carcinogenicity appears to be a dietary concentration of 1 mg/kg heptachlor plus its epoxide - about 0.15 mg/kg bodyweight (WHO, 1984a). Although some experimental mutagenicity studies have produced equivocal findings, results in the standard tests have been essentially negative. On the basis of the lowest level causing no significant effect of 0.06 mg/kg bodyweight/day in the dog an ADI for heptachlor plus heptachlor epoxide of 0.0005 mg/kg bodyweight was set by the FAO/WHO JMPR (FAO/WHO, 1971).

Magos (1989) and Ober et al. (1987b) indicate that heptachlor in most vertebrate fish ranges up to 50 µg/kg with one species caught in the coastal waters of Chile containing 900 µg/kg. For shellfish, less than 10 µg/kg in oysters from USA prior to 1967 (WHO, 1984a) is probably typical.

The evidence for the carcinogenicity of heptachlor to humans is inadequate and the evidence for its carcinogenicity to animals is limited (IARC, 1987). In assessing the carcinogenic risk from heptachlor in seafood, the main consideration is that its carcinogenic activity appears to be specific to mice.

If a 60 kg person ate 150 g/day of fish containing 50 µg/kg heptachlor, only one quarter of the ADI would have been consumed. Given that the evidence indicates carcinogenic activity is specific to mice, such a level of intake would not appear to involve any carcinogenic risk to man.

4.4 Chlordane

This insecticide is a mixture of 26 components of which 14 are distinguishable by the usual chromatographic methods. The main components are alpha- and gamma-chlordane and the most toxicologically significant metabolite is oxy-chlordane. These are the three materials which are normally determined in residues and it should be borne in mind that carcinogenicity studies with experimental animals have often been carried out with technical chlordane.

Studies on rats have shown that chlordane produces liver hypertrophy and liver pathology typical of microsomal enzyme inducers. There was one report of a significant incidence of hepatocellular carcinomas in rats at dietary concentrations of 25 and 50 mg/kg technical chlordane and another report of thyroid follicular adenomas and malignant fibrous histiocytomas at concentrations of 120 mg/kg and higher (WHO, 1984b). Later reading of the pathology of one of the studies with dietary concentrations up to and including 25 mg/kg concluded that, contrary to the earlier report on the study, all of the tumours found were spontaneous and unrelated to chlordane (Khasawinah & Grutsch, 1989). A study in mice with a mixture of alpha and gamma-chlordane produced a statistically significant incidence of hepatocellular carcinomas at dietary concentrations of 30 mg/kg and higher (WHO, 1984b).

A committee of the US National Academy of Sciences reviewing the carcinogenicity data on chlordane found that it was not carcinogenic in rats and that the only target organ site for carcinogenic response in certain strains of mice was the liver (taken from WHO, 1984b). According to IARC (1987) the evidence for the carcinogenicity of chlordane to humans is inadequate and only limited evidence was found for its carcinogenicity to animals. Mutagenicity studies by the standard methods have been negative for chlordane (WHO, 1984b). On the basis of the lowest no-observed-effect-level of 0.05 mg/kg bodyweight/day in the rat, an ADI of 0.0005 mg/kg bodyweight was set by the JMPR (FAO/WHO, 1987).

The limited amount of data at present available (Magos, 1989; Skare et al., 1985; El Dib & Badawy, 1985; WHO, 1984b) indicates that the levels of chlordane in the muscle of vertebrate fish are generally below 100 µg/kg but there is one value of 300 µg/kg. Concentrations in the livers of fish from contaminated waters range from 4-400 µg/kg. The only information on shellfish is that a small proportion of oysters gathered in the South Atlantic, Gulf of Mexico and Hawaii contained up to 40 µg/kg chlordane (WHO, 1984b; IARC, 1979).

In assessing the carcinogenic risk from chlordane in seafood the main consideration is that the carcinogenic potential appears to be typical of other microsomal enzyme inducers and the carcinogenic response peculiar to rodents.

If a 60 kg person ate 150 g/day of fish containing 100 µg/kg chlordane this would constitute half of the ADI. For reasons similar to those given in relation to dieldrin and heptachlor such intakes would not constitute a cancer risk.

4.5 Hexachlorocyclohexane (HCH)

Technical HCH contains a number of isomers of which gamma-HCH (Lindane) is commonly used as an insecticide.

Long-term studies in rats with separate isomers of HCH (alpha, beta, gamma and delta) as well as with technical HCH have been described as giving "inadequate" evidence of carcinogenicity to humans (IARC, 1987). In one study there was a low incidence of hepatocellular carcinomas at dietary concentrations of 1000 and 1500 mg/kg alpha HCH but it is not clear from the data at present available whether these were statistically significant (IARC, 1979). In other studies HCH produced liver nodular hyperplasia and other effects typical of microsomal enzyme inducers. These effects were seen with alpha and gamma HCH but it is not clear whether they occurred with the other isomers.

In a number of studies of mice all of the main isomers and technical HCH produced benign and malignant hepatomas at dietary concentrations above 100 mg/kg. Although most of these studies were too short in duration to give useful no-effect levels it appears probable that dietary concentrations of 50 mg/kg gamma HCH and other isomers would be no-observed-effect levels for liver tumours in mice (IARC, 1979). In one study (Wolff et al., 1987) exposure to a dietary concentration of 160 mg/kg gamma HCH was associated with an incidence of Clara cell hyperplasia and lung tumours as well as with liver tumours in some strains of mice. Mutagenicity studies on alpha, beta and gamma HCH have been essentially negative (IARC, 1987). On the basis of a no-observed-effect-level of 0.75 mg/kg bodyweight/day in the rat, an ADI for gamma HCH of 0.008 mg/kg bodyweight was set by the JMPR (FAO/WHO, 1989). No ADI was established for the other isomers or for technical HCH.

Most information on residues in seafood is on the alpha and gamma isomers but in the Baltic where beta HCH also appears to be present the concentrations of all three isomers are similar (Falandysz, 1986). Most data on the edible parts of vertebrate fish indicate that the concentrations for each isomer are 50 µg/kg or less (Magos, 1989; Eisenberg and Topping, 1985; El Dib & Badawy, 1985; Skare et al., 1985). However, Huschenbeth (1986) gives a value of 180 µg/kg and Ober et al. (1987b) one of 740 µg/kg. Little information is available on the residues of HCH in shellfish; Ober et al. (1987b) give a value of 113 µg/kg.

In assessing the carcinogenic risk from HCH in seafood the main consideration is that the carcinogenic potential appears to be typical of other microsomal enzyme inducers and the carcinogenic response peculiar to rodents.

If a 60 kg person ate 150 g/day of fish containing 50 µg/kg gamma HCH this would constitute $^{1}/_{64}$ of the ADI. Such a level of exposure would not constitute a carcinogenic risk even if the fish contained equal quantities of the other two main HCH isomers.

4.6 Polychlorinated Biphenyls (PCBs)

PCBs are industrial products generally consisting of complex mixtures of chemicals. The main components of the mixtures differ from one another in the numbers and positions of the chlorine atoms on the biphenyl group but the products also differ in the quantities and types of non-biphenyl impurities. These differences occur from batch to batch even within the same technical grade of commercial material.

The biological activities of the main PCB components differ markedly from one another (Safe, 1984) and some of the impurities - particularly 2,3,7,8-tetrachlorodibenzodioxin (TCDD) and 2,3,7,8-tetrachlorodibenzofuran (TCDF) have special and severe toxic properties, especially for small animals such as rodents; inter alia it acts as a potent tumour promoter. A further complication is that, because the components of the PCB mixtures have different environmental mobility and persistence, the material found in residues is unlikely to be the same as materials used in carcinogenicity studies.

In long-term feeding studies in rats, PCBs cause liver nodular hyperplasia which increases with increasing dose and increasing chlorine content of the PCB mixture (reviewed by Safe, 1984). There are a number of reports of hepatocellular carcinomas associated with long-term feeding of dietary concentrations of 100 mg/kg PCB and higher (Schaeffer et al., 1984). Ward (1985), re-examining material from an older study, reported an incidence of about 4% adenocarcinomas of the stomach in rats fed PCB containing 54% chlorine at all dietary concentrations used (25, 50 and 100 mg/kg). No tumours of this type were found in the control group.

PCBs caused liver nodules and hepatocellular carcinomas in mice at dietary concentrations of 300 and 500 mg/kg but the duration of the studies was too short to establish useful no-observable-effect levels (IARC, 1978b).

Mutagenicity studies by the standard methods have been negative for PCBs except for those with low percentages (eg 21%) of chlorine (IARC, 1978b). Some of these form covalent DNA adducts, both in vivo and in vitro, after metabolic activation (Safe, 1989). The more highly chlorinated and planar components act as promoters, possibly by a mechanism similar to that of TCDD.

The short-term effects of human exposure to PCBs have been very well documented from occupationally-exposed workers and from accidental poisoning in Japan and Taiwan. For given serum levels of PCB the effects from the accidental poisoning were very much more serious than those from occupational exposure and it has been suggested (Safe, 1984) that the more serious effects are attributable, in part at least, to contamination by polychlorinated dibenzofurans (PCDF) and other halogenated aromatics. Although the incidence of cancer in the accident victims was higher than expected and a high proportion of those who died had hepatomas, cirrhosis and hepatomegaly (Masuda, 1985) it was considered premature to conclude that the high cancer mortality was associated with the PCB poisoning.

There appears to be no conclusive evidence of increased cancer incidence in the many reports of occupational exposure to PCBs. Brown (1987) reports a statistically significant incidence of cancer of the liver and biliary passages in workers (especially females) exposed to PCBs in the manufacture of electrical capacitors. However, the numbers involved are too small for any but tentative conclusions. Similarly a cluster of three cases of renal adenocarcinoma in young male workers exposed to PCBs (Shalat et al., 1989) is not sufficient to be conclusive of a causal connection). PCBs show limited evidence for carcinogenicity to humans and sufficient evidence for carcinogenicity to animals (IARC, 1987). Because of the limitations of the available data and the ill-defined nature of the materials used in feeding studies, JECFA found it impossible to establish, for PCBs, a tolerable intake value for humans. Some indication of safe exposure levels can be obtained from the no-effect level observed in monkey studies (0.04 mg/kg bodyweight per day (WHO, 1990).

A review of reports of PCBs in seafood (Magos, 1989; Friberg, 1988; Gutenmann et al., 1988; Villeneuve et al., 1987; Huschenbeth, 1986; Falandysz, 1986; El Dib & Badawy, 1985; Skare et al., 1985) indicates a level in the edible parts of vertebrate fish of at least several hundred µg/kg. Sixteen

percent of seafish in Japan contained 1000 µg/kg PCB or more in the edible parts in 1972. Canadian marine fish in 1975 contained up to 2700 µg/kg PCB (IARC, 1978b). In the USA a tolerance level of 5000 µg/kg PCB in fish was set (Maxim & Harrington, 1984) and later reduced to 2000 µg/kg.This lower tolerance continued to be exceeded over wide areas (Mearns, 1988) although bivalves in the same areas were much less contaminated. It appears that the major intake of PCB for whole populations is from fish (Cordle et al., 1982 and Kimbrough, 1987). The available data on shellfish indicates levels of 200 µg/kg or less of PCBs.

PCBs, especially the more highly chlorinated ones, are powerful microsomal enzyme inducers and the major liver carcinogenic effects in rodents reflect this characteristic. However, there are a number of observations which may indicate that PCBs exert a carcinogenic effect by mechanisms other than those common to classical microsomal enzyme inducers such as phenobarbitone. These are:-

- the stomach cancers in rats (Ward, 1985);
- the formation of covalent DNA adducts (Safe, 1989);
- the chromosome damage to cells in vitro (Sargent et al., 1989);
- the evidence, albeit inconclusive, that occupational or accidental exposure is associated with increased cancer incidence.

If a 60 kg person ate 150 g/day of fish containing 2000 µg/kg PCB, this would amount to 5 µg/kg bodyweight per day. This is about $^1/_{30}$ of the estimated average daily intake in the accident in Japan in 1968 which involved about 1000 people (Kimbrough, 1987) and $^1/_8$ of the no-effect level of 0.04 mg/kg bodyweight for monkeys (WHO, 1990). Based on the latest information available, it would be premature to conclude that there is a causal link between cancer mortality and PCB poisoning in the accident in Japan and it is difficult to make inferences concerning PCBs in seafood. Other confounding factors are that the Japanese accident victims consumed polychlorinated quaterphenyl in about the same quantity as PCBs and that their consumption lasted only a few months.

These findings, plus the fact that PCB residues in fish are high and not well-defined chemically, lead to the conclusion that the carcinogenic risk from PCBs in seafood, as distinct from certain carcinogenic impurities often associated with PCB formulations, cannot be assessed at present.

5. Polynuclear aromatic hydrocarbons (PAHs)

PAHs are a group of materials mainly formed by the incomplete combustion of organic materials. Some of the PAHs - mainly those with four to seven fused rings - have been shown to be carcinogenic to experimental animals particularly in skin-painting studies. The carcinogenic properties of PAHs are associated with the characteristics of the molecular structure typified by benz(a)pyrene (BaP).

Very few PAHs have been shown to be carcinogenic by the oral route and among these are 7, 12-dimethylbenz(a)anthracene, benz(a)pyrene, dibenz(ah)anthracene and 3-methylcholanthrene. The malignancies observed in these studies included mammary adenocarcinoma, squamous cell carcinoma of the stomach, spindle cell sarcoma and leukaemia. The studies do not appear to be capable of giving useful no-observed-effect levels (Lo & Sandi, 1978). Few other PAHs appear to have been studied for carcinogenicity by the oral route.

A number of occupational cancers are attributable to exposure to the products of incomplete combustion containing PAHs. However, in spite of the wide-spread occurrence of PAHs in food - particularly smoked and grilled foods, there appears to be no epidemiological evidence that the intake of food containing traces of PAHs makes any appreciable contribution to the risk of human cancer (IARC, 1983). A possible exception is the suggestion that the high incidence of stomach cancer in Iceland may be caused by the high intake of smoked fish and meat (Lo & Sandi, 1978). IARC has found no adequate evidence for carcinogenicity of BaP in humans but sufficient evidence for carcinogenicity in animals and for activity in short-term genotoxicity tests (IARC, 1983, 1987).

No ADIs have been set for the total intake of PAHs but there are some acceptable levels for PAH in drinking water. The US EPA has published an acceptable concentration for BaP in drinking water of 0.028 µg/l. Rugen et al. (1989) proposed that acceptable concentrations of other PAHs should be based on this value but with a factor derived from the relative carcinogenic potency of the individual PAH in experimental animal studies. Depending on how many PAHs can be identified and measured in drinking water the acceptable concentrations would represent a small proportion of the total oral intake of PAHs which is estimated to be 1.6-16 µg per person per day in the USA (WHO, 1984c).

The WHO guideline value for BaP in drinking water is 0.01 µg/l and the daily intake of about 0.02 µg from drinking water represents 0.1% of the total ingested. The typical oral intake of BaP would therefore be about 20 micrograms per person per day. It is suggested that BaP should be taken as an index of all PAH and that limitation of the intake of BaP would reduce the intake of the other PAHs (WHO, 1984c).

Fish from uncontaminated waters usually do not contain detectable amounts of PAH (Lo & Sandi, 1978). Bivalves and crustacea do however accumulate PAHs from contaminated water and, unlike vertebrate fish, appear to be unable to metabolise or excrete the products. Lobsters from contaminated water were found to have 700-1400 µg/kg BaP in the digestive gland and 30-40 µg/kg in the tail muscle. These values declined only slightly when the animals were held for one year in clean water, but when they were boiled some of the PAH migrated from the digestive gland to the tail muscle. Lobsters from an adjacent relatively clean site contained 1.6-8 µg/kg BaP in the digestive gland and 0.5-1.6 µg/kg in the tail muscle (Uthe & Musial, 1986). Concentrations of BaP in shellfish from the different parts of the world range from 0.6 to 2770 µg/kg (Magos, 1989). Oysters from a highly polluted area contained PAHs at the "tens-of-ppm-level". In another area where clams contained about 2000 µg/kg PAHs the crabs and fish contained about one hundredth of these concentrations (Friberg, 1988).

In assessing the cancer risk from PAHs in seafood the major consideration is that some of the products produce a range of carcinogenic responses in different species of experimental animal and by different exposure routes. No clear-cut no-effect levels appear to be available from these studies and some of the products are genotoxic, both in vivo and in vitro. Moreover PAHs are implicated as causal agents in some human cancers although there is no convincing evidence that the PAHs in the human diet increase the cancer risk.

It is concluded that consumption of 150 g/day of fish or shellfish from unpolluted water and containing in the vicinity of 1 µg/kg PAHs would not appreciably increase the average dietary intake of PAHs and would therefore be acceptable. On the other hand consumption of shellfish from highly contaminated waters would appreciably increase the total dietary intake of PAHs and could present an unacceptable cancer risk.

6. Nitrosamines

The nitrosamine group of compounds comprise some of the most powerful carcinogens known. In experimental animals they are active at relatively small doses, usually affect more than one organ and, under experimental conditions, can produce cancer in all species that have been tested (Magee et al., 1976). It is currently suspected that they might also cause cancer in man.

Nitrosamines are formed in seafood as a result of normal cooking (Tsuda et al., 1988; Matsui et al., 1984), salting and smoking (Yu & Henderson, 1987; Poirier et al., 1987) decomposition and simulated gastric digestions (Groenen et al., 1982). Under those conditions, the nitrosamines are formed by the interaction of nitrates/nitrites with amino-acids in the fish. The nitrosamines that are commonly found are nitrosodimethylamine, nitrosodiethylamine, nitrosopiperidine and nitrosopyrrolidine. The amounts of the nitrosamines found in cooked or salted fish can be as high as 177 mg/kg.

In some early studies the levels of nitrosodimethylamine and nitrosodiethylamine found in most samples of fresh or frozen fish and shellfish was of the order of 1 µg/kg, but in some samples, levels were higher (up to 9 µg/kg). These results have been confirmed by a recent study conducted on

various types of fish in Japan. Analysis for nitrosamines reveal that most of the 14 species for fish examined were free of nitrosamines. Exceptions were cod, cuttlefish and salmon which contained 3.5, 2.1, 2.6 µg/kg respectively (IARC, 1978a).

Although one cannot entirely exclude the possibility that those small amounts of nitrosamines are formed in vivo it is much more likely that they are formed after the fish are caught. Fish and probably other seafood are rich in secondary amines. The process of decomposition which commences after harvesting releases those amines which are then nitrosated by the small amounts of nitrate present in sea-water. Any bacteria present or any nitrates added to the fish as a preservative will accelerate this process.

Because of these uncertainties it is not possible to evaluate the contribution of the marine environment to the nitrosamines present in fresh seafood but there is no evidence that marine pollution is a significant factor.

7. Consumption of seafood:- Cancer Risk - Conclusions

This review of the contaminant levels present in fish and shellfish, and the human cancer risk associated with the consumption of relatively large quantities of these foods (150g/day), gives only limited cause for concern. For the five elements considered it is concluded that for cadmium, mercury, nickel and lead marine fish and shellfish consumption does not constitute a significant cancer risk. There appears to be no cancer risk from the arsenic content of fish and shellfish provided, as is usually the case, this is present in the organic form. However, even if present in the inorganic form it is unlikely that the provisional tolerable weekly intake (PTWI) will be exceeded.

In relation to the organochlorine compounds reviewed chlordane, heptachlor and hexachlorocyclohexane (HCH) levels in seafoods are considered not to present a cancer risk. Similarly, although in some areas the degree of contamination by dieldrin (or aldrin) could lead to the acceptable daily intake (ADI) being exceeded, the risk of cancer through dieldrin in seafood is not significant. Whilst the consumption of fish from waters heavily contaminated by DDT is considered undesirable on other health grounds it is not considered to present a cancer risk.

It was not possible to make an assessment for PCBs, because most of the data on PCBs in the literature are for undefined mixtures of PCB congeners. It is however possible that some of the higher concentrations in marine fish and shellfish (ca 2 mg/kg or more) would be unacceptable on other toxicological grounds. No assessment has been made of the possible cancer risk of consumption of seafood containing increased levels of polychlorinated dibenzo-dioxins or dibenzofurans.

Certain polycyclic aromatic hydrocarbons (PAHs) are known to cause cancer in animals and probably man. However, the levels of PAH in most fish do not represent an appreciable source of exposure to humans, relative to other exposure routes. Nevertheless, the consumption of fish or shellfish from heavily contaminated marine areas could appreciably increase total dietary intake and present an unacceptable risk.

The only other group of compounds for which an assessment of cancer risk was made was nitrosamines. Although nitrosamines can be detected in marine fish and shellfish it is considered much more likely that they are formed after the fish are caught from constituents unconnected with marine pollution. Consequently it was not possible to evaluate the contribution of the marine environment to nitrosamine intakes via seafood.

The risk assessments based on ADIs include a reasonable safety factor and it seems unlikely that a significant cancer risk exists through the consumption of marine fish or shellfish, at least for the chemicals assessed in this report. Whilst this conclusion is based on a consumption rate of 150 g/day, which is high by normal standards, certain groups are known to eat 4-5 times this amount on a regular basis and there may be local areas of higher contamination than those assumed in this report. However, unless these two factors coincide, which is unlikely, the overall conclusions are

unaffected. It should be noted, however, that although the chemicals considered were those for which the risks were thought to be greatest, it cannot be excluded that other chemicals may be present which, if assessed might modify the general conclusions of this report. Nevertheless, although the review does not completely clear seafood as a significant source of carcinogens it seems unlikely that such a risk is significant for most compounds.

Table 1.

HISTORIC AND SIGNIFICANT OCCURRENCES OF NEOPLASTIC LESIONS IN BIVALVE MOLLUSCS FROM NORTH AMERICA AND THE PACIFIC BASIN

HOST SPECIES	NEOPLASTIC LESIONS	GEOGRAPHICAL LOCATION	SOURCE
American oyster *Crassostrea virginica*	Hemic germinoma	Atlantic Coast (U.S.)	Couch (1969); Farley (1969a) Newman (1972); Frierman and Andrews (1976); Harshbarger et al. (1977)
C. virginica	Hemic	Gulf Coast (U.S.)	Couch and Winstead (1977); Couch (1984)
Japanese oyster *Crassostrea gigas*	Ganglioneuroma, epithelioma	Pacific Coast (U.S.)	Pauley and Sayce (1967, 1968); Pauley et al. (1968)
C. gigas	Hemic	Japan	Farley (1969a)
Australian Oyster *Saccostrea cucullata*	Epithelioma	Australia	Wolf (1969, 1976)
Ostrea chilensis	Hemic	Chile	Mix and Breese (1980)
Bay Mussel *Mytilus edulis*	Hemic	Pacific Coast (Canada)	Farley (1969b); Mix (1982, 1983)
M edulis	Hemic	Pacific Coast (Canada)	Emmett (1984; Cosson-Mannery et al. (1984)
Softshell clam *Mya arenaria*	Hemic, germinoma	Atlantic Coast (U.S.)	Yevich and Barszcz (1976); Brown et al. (1977); Harshbarger et al. (1977); Cooper et al. (1982); Farley et al. (1986)
Clam *Macoma balthica*	Gill carcinoma	Atlantic Coast (U.S.)	Christensen et al. (1974)
M. nasuta	Hemic	Pacific Coast (U.S.)	Farley (1976)
Hard clam *Mercenaria mercenaria*	Germinoma	Atlantic Coast (U.S.)	Yevich and Barry (1969); Barry and Yevich (1972, 1975)

Table 2.

HISTORIC AND SIGNIFICANT OCCURRENCES OF NEOPLASTIC LESIONS IN MARINE BONY FISHES FROM NORTH AMERICA AND THE PACIFIC BASIN

HOST SPECIES	NEOPLASTIC LESIONS	GEOGRAPHICAL LOCATION	SOURCE
Genyonemus lineatus (white croaker)	oral papillomas, epidermal papillomas, hepatic neoplasms	Southern California	Russell and Kotin (1957); Young (1964); Mearns and Sherwood (1974, 1977) Malins et al. (1988)
Microstomus pacificus (Dover sole)	epidermal papillomas	Southern California	Young (1964); Means and Sherwood (1977)
Mugil cephalus stripped mullet)	fibrosarcoma	Northern Gulf of Mexico	Edwards and Overstreet (1976)
Pleuronectids (flatfish)	epidermal papillomas; lesions of internal organs, inlc. hepatic neoplasms	Puget Sound	Stich et al. (1976); McCain et al. (1977, 1982, 1988); Pierce et al. (1978); Malins et al. (1980, 1982, 1984, 1988); Myers (1987)
Pleuronectids (flatifish)	epidermal papillomas	Japan, Hokkaido Island	Oishi et al. (1976); Stich et al. (1977a 1977b)
Microgadus tomcod (Atlantic tomcod)	hepatic neoplasms	Hudson River estuary	Smith et al. (1979)
Microgadus proximus (Pacific tomcod)	hepatic neoplasms	Puget Sound	Malins et al. (1980 1982)
Nibea mitsukurii (nibe croaker)	chromatophoromas	Japan	Kimura et al. (1984)
Leptocottus aramatus (Pacific staghorn sculpin)	hepatic neoplasms	Puget Sound	Malins et al (1984)
Fundulus grandis (Gulf killifish)	chromatophoroma	Northern Gulf	Couch (1985)
Pseudopleuronectes americanus (winter flounder)	hepatic neoplasms	Boston Harbor	Murchelano and Wolke (1985)

Table 3.

Chemicals, groups of chemicals, and industrial processes recognized by IARC (1987) as carcinogenic to humans (Group 1):

4-Aminobiphenyl	Diethylstilboestrol
Arsenic and certain arsenic compounds	Underground haematite mining
Asbestos	Manufacture of isopropyl alcohol by the strong acid process[1]
Manufacture of auramine[1]	Melphalan
Benzene	Mustard gas
Benzidine	2-Naphthylamine
N,N-bis (2-chloroethyl)-2-naphthylamine (chlornaphazine)	Nickel refining[1]
Bis(chloromethyl)ether and technical grade chloromethyl methyl ether	Soots, tars and mineral oils
Chromium and certain chromium compounds[1]	Vinyl chloride

[1]The specific compound(s) which may be responsible for a carcinogenic effect in humans cannot be specified precisely.

Table 4. Spectrum of Agents and Agent Types Tested in Fish Carcinogen Systems

Compounds	Representative References
Aromatic Amines	Pliss & Khudoley, 1975; Sato et al., 1973
Acetylaminofluorene (+)[1]	
Azo Compounds	Halver, 1967; Hatanaka et al., 1982; Pliss Khudoley, 1975
o-aminoazotoluene (+)	
4-dimethylaminoazobenzene (+)	
aminotriazole (-)	
Halogenated Organic Compounds[2]	
Bis(2-chloroethyl)ether (s)	Halver, 1967; Hawkins et al., in press; Walker et al., 1985
Bromodichloromethane (m)	
Bromoform (m))	
Carbon tetrachloride (m, s) (+))	
Chlorodibromethane (m)	
Chloroform (m)	
Dichlorodiphenyltrichloroethane (DDT) (s) (+)	
Ethylene dichloride (s)	
Pentachlorophenol (s)	
Trichloroethylene (m, s)	
Vinylidene chloride (s)	
Mycotoxins	Doster et al., 1972; Halver, 1967; Hatanaka et al., 1982; Hendricks et al., 1978, 1980a,b,c,d,e,f;Matsushima & Sugimura, 1976; Sato et al., 1973; Schoenhard et al., 1981; Sinnhuber et al., 1974; Wales & Sinnhuber, 1972; Wolf & Jackson, 1967.
Alfatoxin B-1 (+)	
Alfatoxin G-1 (+)	
Alfatoxin L/L-1 (+)	
Alfatoxin M-1 (+)	
Alfatoxin Q-1 (+)	
Sterigmatocystin (+)	
Versicolorin A (+)	
Ochratoxin A & B (-)	
N-Nitroso Compound	Ahydrin & Bulay, 1983; Couch & Courtney, 1987; Egami et al., 1981; Halver, 1967; Hatanaka et al., 1982; Hendricks, 1981, 1982; Hendricks et al., 1980b, 1984; Ishikawa, et al., 1975;
N-nitrosodiethylamine (+)	
N-nitrosododimethylamine (+)	
N-N'-dinitrosopiperazine	

Nitrosomopholine (+) N-methyl-N-nitrosourea (+) N-ethyl-N-nitrosourea (-) dibutylnitrosamine (-) N-methyl-N-nitro-N-nitrosoguanidine (+)	Khudoley, 1984; Kimura et al., 1981, 1982-83, 1984; Klaunig et al., 1984; Koenig & Chasar, 1984; Kyono-Hamaguchi, 1984; Pliss & Khudoley 1975; Sato et al., 1973 a,b; Schultz & Schultz, 1984; Simon & Lapis, 1984; Stanton, 1965.
Plant Derivatives Bracken (-) Cycloipropenoid fatty acids (+) Cycad nut meal (+) Cysasin (-) Gossypol (-) Methylazoxymethanol acetate (+) Pyrrolizidine (Senecio) alkaloids (-)	Aoki & Matsudaira, 1977, 1984; Fournie et al. 1987; Hawkins et al., 1985a,b, 1986; Hendricks et al., 1980c,d, 1981a, 1983 1984; Herman, 1970; Lee et al., 1968 1971; Matsushima et al., 1975; Schoenhard et al., 1981, Sinnhuber et al., 1976; Stanton, 1965.
Polynuclear Aromatic Hydrocarbons Benzo(a)pyrene (+) dimethylbenze(a)anthracene (+) 3-methylcholabthrene (+)	Ermer, 1970, Hendricks et al., 1982, Kimura et al., 1984; Pliss & Khudoley, Schultz & Schultz, 1984
Misc. Compounds β-aminoproprinoitrile (-) Aroclor 1254 Benzidine (?) Carbarzone (+) Diethylstilbestrol (+) Nifuropirinol (+) Tannic acid (+) Thioacetamide (-) Thiourea (+) Trifluralin (-) Urethane (+)	Couch et al., 1981; Halver, 1967; et al., 1980a, 1981b; Kimura et al., Kimura et al., 1984; Levy, 1962; Martin, Martin, 1982; Pliss & Khudoley, 1975

[1](+) - neoplasia experimentally induced in one or more fish species.
(-) - no neoplastic lesions experimentally induced.
(?) - possible neoplastic lesions, but results equivocable
[2]Agents tested singly (s) or in mixtures (m)

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