Retinoids in marine mammals and their use as biomarkers of organochlorine compounds

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ABSTRACT

Retinoids, also known as vitamin A, are non-endogenous molecules that are essential for a number of physiological processes in mammals. Imbalance of retinoids has been associated with reproductive impairment, embryonic mortality, growth retardation and bone deformities, pathologies in skin and the nervous system, and immune suppression. Mammals cannot produce retinoids so their primary source is dietary. They are absorbed by the small intestine and packaged as retinyl esters in chylomicrons, which enter the circulation and end up mostly in the liver and fatty tissues. Plasma retinoid levels are homeostatically regulated, so they remain constant despite variations in dietary supply or tissue stores. Therefore body depletion of retinoids cannot be reliably assessed through levels in blood, and should be evaluated through concentrations in depot tissues. In marine mammals, the main storage sites for retinoids are liver and blubber. Although not a universal rule, the concentration of retinoids often increases with age in both sexes because of progressive build-up of retinyl esters. In addition, sex often affects retinoid levels, but the nature and magnitude of this effect varies between species and populations. Taxonomic, life-style (particularly dietary) and climatic differences may explain dissimilarities in the effect of age and sex on retinoid levels. For this reason, retinoids can be used to distinguish populations or population components showing distinct dietary, behavioural, or other traits. Disease, particularly when affecting organs of physiological importance or inducing malnutrition, may affect retinoid tissue levels, so care should be taken when studying concentrations in stranded animals. Organochlorine compounds, particularly PCBs, dioxin (TCDDs) and DDTs, increase mobilisation of retinoids from hepatic and extrahepatic storage sites into serum, accompanied by enhanced degradation and elimination of retinoids through urine. In terrestrial mammals, this effect increases retinoid concentration. Conversely, in some species of marine mammals plasma retinoid levels have been reported to decrease when exposure to organochlorines increases, although the physiological mechanisms are unclear. However, given the homeostatic regulation of retinoids in blood, variation in plasma is expected to be less than that in liver or blubber. Because retinoid tissue levels vary in marine mammals even at moderate exposure to organochlorines, and original levels are restored when such exposure decreases or disappears, retinoids may be used as a biomarker of the impact of pollutants on populations. Further research is needed to validate their use, particularly in cetaceans.

KEYWORDS: MARINE MAMMALS; RETINOL; ORGANOCHLORINES; BIOMARKERS

INTRODUCTION

Marine mammals is referred to.

Chemical structure of retinoids

Retinoid is a general term referring to a group of closely related compounds whose molecular structure consists of four isoprenoid units joined in a head-to-tail manner. This definition includes compounds such as retinol and retinol derivatives, retinal, retinyl palmitate and retinoic acid.

All-trans-retinol (vitamin A alcohol) is the parent vitamin A compound. It is a fat-soluble primary alcohol of low molecular weight (mw = 286). The aldehyde form, retinal, is found in the retina of the eye, and retinoic acid, a metabolite of vitamin A, is highly active in a number of physiological processes (Wolf, 1984).

Physiology of retinoids

Although retinoids can be toxic in high concentrations and the adverse effects of hypervitaminosis are documented in both man and animals (Armstrong et al., 1994), in natural conditions the most frequent disorders and pathological effects are produced by low availability of the compound.

Retinoids play an important role in: vision (xerophthalmia and night blindness are both symptoms of its deficiency); the maintenance of the reproductive, endocrine and immune systems; growth and foetal development; and the regulation of the proliferation and differentiation of many cell types. Thus, imbalance of retinoids has been associated with a diversity of anomalies, including reproductive impairment, embryonic mortality, growth retardation and bone deformities, pathologies in skin and the nervous system, and immune suppression (Thompson, 1976; Peakall, 1992). Many of these effects are mediated by the action of retinoc
acid on gene expression (Blomhoff et al., 1991). In addition, retinoids have a protective effect against the development of various cancers (Wolf, 1984).

For mammals, none of which can synthesise retinoids, vitamin A is an essential nutrient. Dietary retinoids are available from two sources: from plants in the form of provitamin A precursor compounds, namely β- (mainly), α- and γ-carotene and cryptoxanthin; and from animal tissues as long-chain retinyl esters.

Once in the digestive system, retinoids are absorbed by the small intestine and packaged as retinyl esters in chylomicrons, which enter the circulation and are taken mostly by the liver. In this organ, chylomicrons are metabolised and retinyl esters are processed for hepatic storage or for secretion as retinol bound to retinol binding protein or RBP (MW = 21000) (Blomhoff, 1994; Green and Green, 1994).

RBP delivers plasma retinoids to target tissues throughout the body (Soprano and Blaner, 1994). Over 95% of RBP-retinol circulates in the blood as a 1:1 molar complex with a second transport protein called transthyretin or TTR (MW = 54980), which also transports thyroid hormones TT4 (Blomhoff, 1994; Green and Green, 1994). It has been established that retinoids recycle among plasma, liver and extrahepatic tissues, since the plasma retinoid turnover is more than one order of magnitude greater than the utilisation rate. The vehicle for retinoid recycling is RBP (Blomhoff et al., 1992; Sommer and West, 1996).

Plasma retinoid levels are constant despite great variation in dietary supply or in liver and extrahepatic tissues stores. Thus, it appears that plasma retinoid levels are homeostatically regulated, ensuring that retinoids are continuously available to vitamin A-dependent cells (Wolf, 1984). As a consequence, body depletion of retinoids cannot be assessed through circulating levels in blood, but should be evaluated through concentrations in depot tissues such as liver and fat. The excretion of retinoids in the urine does not appear to be affected by the retinoid status of the animal itself but by the amount of retinoids available through the diet (Raila et al., 2000).

**STORAGE OF RETINOIDS IN TISSUES**

The comparative tissue distribution of retinoids in mammals has not been studied systematically. However, surveys available for terrestrial species usually point to the liver as the main storage site, with 50-80% of the body load commonly present in this organ. Extrahepatic tissues such as kidneys, adipose tissue, lung or testis, can also play a significant role in the storage and mobilisation of these compounds (Blaner and Olson, 1994). However, there are dissimilarities among species and/or taxonomic groups. For example, in the Canidae and Mustelidae families, retinoid concentrations in plasma are about 10-50 times higher than in other mammals; indeed, in many mammals such a high level would reflect hypervitaminosis A (Schweigert et al., 1990; 1991b). Kidney retinoid concentration in canids is also high and far exceeds those in the liver; such low hepatic levels would normally be considered an indication of severe vitamin A deficiency in other mammals (Underwood, 1984; Schweigert and Buchholz, 1995). It should be pointed out that the urine of canids contains both retinol and retinyl esters (Schweigert et al., 1991a), while that of human and rams only contains metabolic forms of retinoids, such as retinyl acetate (Schweigert and Buchholz, 1995). Therefore, the high level of retinoids observed in the kidney of at least the canids can be associated with this particular form of excretion (Schweigert and Buchholz, 1995). As stated above, generally in terrestrial mammals, the concentration of retinoids in blood is kept constant homeostatically and it decreases only when storage tissues are severely depleted (Wolf, 1984; Blomhoff et al., 1992).

Information on the distribution of retinoids in the body of marine mammals is limited to a few studies that report the concentration in selected tissues from the same individuals (Table 1). There are some data on concentrations in isolated tissues, but these cannot be compared between studies because of substantial variation at individual, population and species levels (see below). The information available suggests that, as is usual in terrestrial mammals, retinoids are extensively stored in the form of retinyl esters in the liver. Indeed, it has long been known that the liver of cetaceans is extremely rich in retinoids (Schmidt-Nielsen et al., 1934), and the interest in obtaining this compound for commercial production of vitamin A led a number of researchers during the first half of the century to investigate its contents in the tissues of large whales (e.g. Klem, 1935; Wetslesen, 1938; Braekkan, 1948; Ishikawa et al., 1948; 1951; Kaneko, 1948; Mori and Saiki, 1950; Tawara and Fukazawa, 1950a; b). A similar richness in hepatic retinoids was later confirmed in pinnipeds (Rodahl and Davies, 1949; Schweigert et al., 1987; Ball et al., 1992; Schweigert and Buchholz, 1995; Käkela and Hyvärinen, 1997; Käkela et al., 1997).

However, in marine mammals, blubber is also a significant storage site of retinoids and the concentration of retinoids in the blubber of at least some marine mammals appears to be higher than in comparable fatty tissues of man and other terrestrial mammals (Schweigert et al., 1987). Thermoregulatory and lipid storage needs render fatty tissues of marine mammals to be a substantial proportion of body mass, usually in the range 15-55% and, given the lipophilic nature of retinoids, this allows for massive accumulation of these compounds. The blubber/body mass ratio in marine mammals is inversely scaled, so smaller species tend to have a larger contribution of fatty tissues, and therefore larger relative retinoid stores, than larger species (Ryg et al., 1990; 1993; Aguilar et al., 1999). In grey seals (Halichoerus grypus), Schweigert et al. (1987) have estimated that blubber accounts for about 40% of total body reserves of retinoids. Borrell et al. (1999) found that blubber is also a significant site for retinoid deposition in harbour porpoises (Phocoena phocoena) from West Greenland.

Information on retinoid levels in tissues or body organs other than liver and blubber is fragmentary. Mori and Saiki (1950) reported concentrations in the intestine of sperm whales (Physeter macrocephalus), Iida et al. (1998) in muscle of Antarctic minke whales (Balaenoptera acutorostrata), Gregory et al. (1955) in the milk of blue whales (B. musculus), and Rosas and Lehti (1996) in the milk of Amazon river dolphins (Inia geoffrensis). However, the sample size in these studies was extremely small, often limited to a single individual, and they offer no reliable insight into individual variation. Studies in harp seals (Pagophilus groenlandicus), grey seals and common seals (Phoca vitulina) indicate that other tissues such as kidneys, lung, retina, pancreas and spleen also have minor shares of the retinoid body content (Rodahl and Davies, 1949).

**MAIN FACTORS AFFECTING VARIATION IN TISSUE CONCENTRATIONS**

As stated above, retinoids are regulated within individual organisms. However biological traits (e.g. sex, age, diet and body condition, incidence of disease, occurrence of
lactation) and anthropogenic influences (e.g. environmental pollutants) have a substantial effect on tissue levels and body content of retinoids.

**Age**

The influence of ageing on retinoids status in terrestrial mammals has been widely studied. Many authors reported an increase in concentrations with age: e.g. liver and blood of rats (Blomhoff et al., 1988); plasma of Florida panthers, *Felis concolor oxyri* (Dunbar et al., 1999) and man (Malvy et al., 1993; Stephenson and Gildengorin, 2000), and in the kidney of dogs (Schweigert et al., 1998). However, other surveys revealed either no trend in retinoid levels between age classes, or even decreasing ones. For example, Garry et al. (1987) found similar plasma retinoid levels in young and old humans, and Savage et al. (1999) reported that age did not affect plasma levels of retinoids in free-ranging African elephants (*Loxodonta africana*). A decrease in serum retinoids was observed by Succari et al. (1991) in humans and by Shrestha et al. (1998) in female Nepalese elephants (*Elephas maximus*).

Similarly, studies on pinnipeds and cetaceans (Table 2) do not produce consistent results. While many populations showed, both in the liver and in the blubber, an increasing trend in retinoid concentrations with age, others revealed no apparent trend or even a decreasing tendency with age. This variation could not be explained by inter-specific, inter-population or even inter-tissue differences. For example, the studies on ringed seals (*Pusa hispida*) from Lake Saimaa by Käkelä et al. (1997) showed a significant positive age-related trend in the blubber and a negative trend in the liver, while those conducted on the same species by the same research group and with an identical sample size (*n* = 12) in Spitsbergen showed the opposite result: a negative trend in the blubber and a positive trend in the liver, although in this case the correlation was non-significant (Table 2).

However, although a general, consistent pattern cannot be deduced from the information available, an increasing trend was the most common finding. This relationship appears to be the result of a decrease in the circulatory clearance of retinoids and other liposoluble compounds with age, coupled with an excess intake of retinoids via diet, which leads to a

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**Table 1**

Distribution of retinoids (mean ± SD) in plasma (µg/ml) and other tissues (µg/g tissue) of marine mammals. Only surveys reporting concentrations in more than one tissue have been included (see text).

<table>
<thead>
<tr>
<th>Species</th>
<th>Location</th>
<th>Age/Sex (M/F)</th>
<th>n</th>
<th>Liver</th>
<th>Blubber</th>
<th>Serum</th>
<th>Kidney</th>
<th>Lung</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harp seal</td>
<td>Newfoundland</td>
<td>Adult</td>
<td>1</td>
<td>720</td>
<td>3.6</td>
<td>-</td>
<td>1.8</td>
<td>0.9</td>
<td>Rodahl and Davis, 1949</td>
</tr>
<tr>
<td>Grey seal</td>
<td>Pembrokestone</td>
<td>Juvenile</td>
<td>1</td>
<td>465</td>
<td>1.074</td>
<td>-</td>
<td>4.725</td>
<td>0.75</td>
<td>Rodahl and Davis, 1949</td>
</tr>
<tr>
<td>Grey seal</td>
<td>Sable Island</td>
<td>Adult M</td>
<td>12</td>
<td>502.6 ± 314.9</td>
<td>33.7 ± 10.9</td>
<td>0.26 ± 0.057</td>
<td>-</td>
<td>-</td>
<td>Schweigert et al., 1987</td>
</tr>
<tr>
<td>Grey seal</td>
<td>Sable Island</td>
<td>Adult F</td>
<td>5</td>
<td>264.9 ± 118.4</td>
<td>62.4 ± 3.7</td>
<td>0.41 ± 0.085</td>
<td>-</td>
<td>-</td>
<td>Schweigert et al., 1987</td>
</tr>
<tr>
<td>Grey seal</td>
<td>Sable Island</td>
<td>Juvenile</td>
<td>21</td>
<td>375.7 ± 320.6</td>
<td>21.9 ± 14.8</td>
<td>0.21 ± 0.068</td>
<td>-</td>
<td>-</td>
<td>Schweigert et al., 1987</td>
</tr>
<tr>
<td>Grey seal</td>
<td>Sable Island</td>
<td>Adult M</td>
<td>6</td>
<td>609 ± 395</td>
<td>45 ± 10</td>
<td>0.2 ± 0.1</td>
<td>8 ± 3</td>
<td>-</td>
<td>Schweigert and Buchholz, 1995</td>
</tr>
<tr>
<td>Harbour seal</td>
<td>Wash</td>
<td>Juvenile</td>
<td>1</td>
<td>27</td>
<td>Not detected</td>
<td>-</td>
<td>0.27</td>
<td>0.18</td>
<td>Rodahl and Davis, 1949</td>
</tr>
<tr>
<td>Ringed seal</td>
<td>Baltic Sea</td>
<td>Adult</td>
<td>7</td>
<td>175.3 ± 32.6</td>
<td>21.6 ± 3.4</td>
<td>-</td>
<td>-</td>
<td>Käkelä et al., 1997</td>
<td></td>
</tr>
<tr>
<td>Ringed seal</td>
<td>Lake Ladoga</td>
<td>Juvenile</td>
<td>4</td>
<td>36.1 ± 7.6</td>
<td>3.1 ± 0.5</td>
<td>-</td>
<td>-</td>
<td>Käkelä et al., 1997</td>
<td></td>
</tr>
</tbody>
</table>

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**Table 2**

Age trends in retinoid concentrations observed in tissues of marine mammals. * = only females; ** = significant p<0.05; * = statistics not performed; ↑ = positive trend; ↓ = negative trend.

<table>
<thead>
<tr>
<th>Species</th>
<th>Location</th>
<th>n</th>
<th>Liver</th>
<th>Blubber</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australian fur seal</td>
<td>Australia</td>
<td>24*</td>
<td>↑**</td>
<td></td>
<td>Southcott et al. 1974</td>
</tr>
<tr>
<td>(Arctocephalus forsteri)</td>
<td></td>
<td></td>
<td></td>
<td>↑**</td>
<td></td>
</tr>
<tr>
<td>Grey seals</td>
<td>Sable Island</td>
<td>65</td>
<td>↑ &quot;</td>
<td>↑ &quot;</td>
<td>Schweigert et al. 1987</td>
</tr>
<tr>
<td>(Halichoerus grypus)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hooded seals</td>
<td>Newfoundland</td>
<td>60</td>
<td>↑ &quot;</td>
<td></td>
<td>Rodahl and Davis, 1949</td>
</tr>
<tr>
<td>(Cystophora cristata)</td>
<td></td>
<td></td>
<td></td>
<td>↑ &quot;</td>
<td></td>
</tr>
<tr>
<td>Harp seal</td>
<td>Newfoundland</td>
<td>145</td>
<td>↑ &quot;</td>
<td></td>
<td>Rodahl and Davis, 1949</td>
</tr>
<tr>
<td>(Pagophilus groenlandicus)</td>
<td></td>
<td></td>
<td></td>
<td>↑ &quot;</td>
<td></td>
</tr>
<tr>
<td>Ringed seals</td>
<td>Lake Saimaa</td>
<td>12</td>
<td>↓***</td>
<td>↑**</td>
<td>Käkelä et al. 1997</td>
</tr>
<tr>
<td>(Pusa hispida)</td>
<td></td>
<td></td>
<td></td>
<td>↑ &quot;</td>
<td></td>
</tr>
<tr>
<td>Ringed seals</td>
<td>Spitsbergen</td>
<td>12</td>
<td>↑</td>
<td>↓</td>
<td>Käkelä et al. 1997</td>
</tr>
<tr>
<td>(Pusa hispida)</td>
<td></td>
<td></td>
<td></td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Ringed seals</td>
<td>Baltic Sea</td>
<td>9</td>
<td>↓</td>
<td>↓</td>
<td>Käkelä et al. 1997</td>
</tr>
<tr>
<td>(Pusa hispida)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harbour porpoise</td>
<td>Greenland</td>
<td>100</td>
<td>↑</td>
<td></td>
<td>Borrell et al., 1999</td>
</tr>
<tr>
<td>(Phocoena phocoena)</td>
<td></td>
<td></td>
<td></td>
<td>↑</td>
<td></td>
</tr>
</tbody>
</table>
build-up of retinyl ester concentrations with age (Maiani et al., 1989; Krasinski et al., 1990). Although it is not clear why some species or populations do not show this general trend, taxonomic, life-style (particularly dietary) and climatic differences may be responsible.

Sex
Information on sex-related variation in retinoids is even more sparse and less consistent than that for age. In terrestrial mammals, no gender-related differences were observed in circulating concentrations of retinoids in black rhinoceros, *Diceros bicornis* (Ghebremeskel et al., 1988), serum levels in free-ranging African elephants (Savage et al., 1999) or liver and serum concentration in humans (Raica et al., 1972; Succari et al., 1991). Conversely, circulating retinoid levels were reported to be higher in female Florida panthers (Dunbar et al., 1999) but lower in females in some human populations (Krasinski et al., 1989; Stephenson and Gildengorin, 2000). These inter-specific differences may be produced by dissimilarities in types of diet and source of retinoids.

In marine mammals, studies on pinnipeds have often suggested sex-related differences although these varied among tissues and species (Fig. 1). Levels of retinoids were found to be higher in the blubber of adult female grey seals (Schweigert et al., 1987) and in the liver of adult female Australian fur seals (Arctocephalus forsteri) (Southcott et al., 1974) than in the corresponding tissues of adult males. However, other surveys have shown the reverse trends. Thus, Rodahl and Davies (1949) found higher concentrations in the liver of male hooded and harp seals than in those of females, and Schweigert et al. (1987) found a similar difference in the liver of grey seals. In cetaceans, the only available survey refers to harbour porpoises, in which no significant differences were found between the blubber retinoid concentrations of males and females (Borrell et al., 1999).

It has been suggested that mothers transfer retinoids to their calves during lactation (Simms and Ross, 2000), which would explain the lower levels in the liver of adult females (Schweigert et al., 1987). Milk is a source of essential nutrients, including retinoids. Although studies are limited, marine mammals appear to have relatively higher levels of retinoids in their milk than terrestrial mammals. However, this appears to be due to the high lipid content of the milk in pinnipeds and cetaceans because, when concentrations are expressed as quantity per unit lipid, levels are of the same order of magnitude or even lower than in terrestrial mammals (Schweigert and Stobo, 1994; Debier et al., 1999). Irrespective of this, during lactation, females of both cetaceans and pinnipeds mobilise a large proportion of their blubber reserves, including the blubber-associated retinoid stores. This explains why during lactation, unlike humans, marine mammals may have high levels of circulatory retinoids coupled with lowered stores of retinoids in the blubber and probably other tissues (Schweigert et al., 1987). However, no explanation has been put forward to explain the higher concentrations of males reported in some studies.

Similarly to the age-related variation, it is likely that taxonomic, dietary and life-style dissimilarities between sexes are responsible for sex-related variations. Reproductive activity may be particularly significant in adult individuals because it often involves changes in hormone levels, behavioural traits and diet (see below).

**Di**et and nutritive condition
Since retinoids are incorporated via food, diet affects tissue levels. However, it is unknown, even in man and laboratory animals, whether body stores of retinoids change as a function of long-term intake of these compounds (Ascherio et al., 1992; Booth et al., 1997; Scrofano et al., 1998). As mentioned above, retinoids in blood are homeostatically controlled when liver stores are sufficient and therefore they only respond to extreme situations, for which reason diet has not been observed to have an effect on them (Blaner and Olson, 1994).

In marine mammals, information on the influence of diet on retinoid status is limited to the study by Kikël et al. (1997), who reported differences in liver and blubber levels between freshwater and marine ringed seals and attributed them to food quality. Differences in diet, as well as climatic or photoperiod dissimilarities may explain variations in retinoid levels between allopatrid populations of the same species. However, such differences may also occur between different components within a single population. For example, variation in diet associated with age, sex or

![Fig. 1. Sex related variation in retinoid levels (µg/g) in liver and blubber of different marine mammal species. Key: HP = Harbour porpoise; GS = Grey seal; AFS = Australian fur seal; HS = Harp seal; HoS = Hooded seals. References: 1Borrell et al., 1999; 2Schweigert et al., 1987; 3Soutcott et al., 1974; 4Rodahl and Davies, 1949.](image-url)
The reproductive condition has been reported for many cetaceans and pinnipeds (Seaman et al., 1982; Perez and Mooney, 1986; Stewart and Murie, 1986; Bernard and Hohn, 1989; Recchia and Read, 1989; Rodhouse et al., 1992; Smith and Read, 1992; Clarke et al., 1993). Retinoids thus have the potential to be used to distinguish populations or population components with distinct dietary, behavioural or other traits, provided that the natural sources of variation are properly controlled.

The effect of nutritive condition on retinoid levels is difficult to assess. Neither Rodahl and Davies (1949) or Borrell et al. (1999), found any significant effect of condition on the retinoids present in the liver and blubber of hooded and harp seals, or in the blubber of harbour porpoises, respectively. Nevertheless, this conclusion should be treated with caution. The sample examined by Borrell et al. (1999) was mainly composed of healthy individuals. While in these conditions, retinoid tissue distribution may remain unaltered. It may require situations of food shortage, massive fat mobilisation (e.g. during migration in large baleen whales or during intense lactation in some phocids), or starvation caused by disease or other condition, for retinoids to be significantly mobilised, redistributed or excreted. This may be particularly relevant for stranded cetaceans, often found in poor nutritive condition.

The tissue vitamin concentration reflects the essential amounts of these substances necessary for enzymatic and metabolic pathways, coupled with any excess picked up from the environment. The establishment of baseline values of retinoid concentrations is a requisite for the understanding of the chronic effects of toxicity and deficiency (Gelatt et al., 1999).

**Disease**

Disease, particularly when it affects organs of physiological importance or induces malnutrition, may affect tissue levels of retinoids. However, the information available on this is restricted to humans. Patients suffering from acute or chronic diseases of the liver such as hepatitis, cirrhosis and hepatic tumours have markedly reduced serum levels of RBP and retinoids. Those affected by significant renal disease also show disorders in RBP and retinoid transport, since the kidneys are a major site for RBP catabolism; thus, levels of retinoids increase when excretion is reduced as a consequence of renal tubular damage or reduced glomerular filtration rate of retinol RBP (Goodman, 1984). In addition, sub-normal serum concentrations of RBP and retinoids have been found in patients with a variety of cancers, but it is not clear whether this is a result of protein or energy denutrition (Soprano and Blaner, 1994).

No information is available on disease and retinoids in marine mammals. Given that disease may affect retinoid tissue levels, data from stranded animals in which disease is suspected should not be included in surveys of retinoid status.

**EFFECT OF ORGANOCHLORINE POLLUTANTS ON RETINOIDS**

Organochlorine compounds can alter retinoid metabolism. However, the biochemical pathway and intensity of the toxic effect appears to vary among species (Håkansson et al., 1991a; Zile, 1992). In general, exposure to PCBs, dioxin (TCDDs) and DDTs leads to depletion of retinoid reserves in mammalian tissues due to increased mobilisation of retinoids from storage sites, especially the liver, and a subsequent increase in their degradation rate (Kelley et al., 2000).

In terrestrial mammals (e.g. rats, otters, minks) feeding on a diet containing toxic organochlorine compounds, the retinol and retinyl ester concentrations in several body organs (liver, depot fat, intestine, lungs and adrenals) have been found to be lower in sample groups exposed to organochlorines than in non-polluted groups. (Brunström et al., 1991; Håkansson et al., 1992; Zile, 1992; Cha et al., 1996; 1998; Murk et al., 1998; Kälkä et al., 1999; Nilsson et al., 2000; Rolland, 2000; Simpson et al., 2000). In contrast, the concentration of retinoids in kidney and, to a lesser extent, in serum, generally increased (Brouwer et al., 1989a; Jurek et al., 1990; Håkansson et al., 1991a; b; Van Bregen et al., 1994a; b; Nilsen et al., 1995; Nilsen et al., 2000). This indicates that organochlorines increase mobilisation of retinoids from hepatic and extrahepatic storage sites into serum, accompanied by enhanced degradation and renal elimination of retinoids through urine (Kelley et al., 1998; 2000). Studies on coplanar PCBs and TCDDs have shown that the toxic effect of these compounds is positively correlated with their ability to bind the Ah (arylhydrocarbon) receptor, causing the induction of cytochromes P-450 1A1 and 1A2 (Pelissier et al., 1992; Brouwer, 1995). Thus, it appears that the mixed-function oxidases containing the cytochrome P450s are particularly active in metabolising retinoic acid (Roberts et al., 1979; Ikegami et al., 1991). Moreover, Roberts et al. (1992) reported that many rabbit liver cytochrome P-450 isoforms including 2A4, 1A2, 2E1, 2E2, 2C3, 2G1 can catalyse the 4-hydroxylation of both retinol and retinaldehyde. These findings indicate that the decrease in hepatic retinoids storage is related to the induction of cytochrome P-450 and retinoid metabolism. In laboratory animals exposed to individual PCB congeners, the order of potency in causing reductions in the hepatic contents of retinoids was: PCB 126 > PCB 77 > PCB 153. This order of potency was found to be positively correlated with the ability of each congener to induce cytochrome P450 and with its toxicity measured as weight loss and thymic involution (Chen et al., 1992; Håkansson et al., 1994). In addition, exposure to organochlorines also inhibits the intestinal absorption of ingested vitamin A, thus exacerbating the imbalance produced by the previous effects (Bank et al., 1989).

However, the retinoid depletive effect of these toxic organochlorines can not simply be extrapolated to all organochlorine forms or derivatives. For example, long-term (1 year) experiments conducted with mink fed with methylsulfonyl-PCBs, which are not very AhR-active, did not reveal any effect on retinoid concentrations in tissues (Lund et al., 1999).

Given the evolutionary basis of the physiological processes involved, most of these effects can probably be extended to marine mammals. However, the specific pathways or dynamics may be somewhat different. Thus, most of the studies so far undertaken in three species of pinnipeds and the polar bear (Table 3) have shown a decrease in plasma retinoids when PCB or other organochlorine (OCs) loads increased (Brouwer et al., 1989b; De Swart et al., 1994; Jensen et al., 1995; Beckmen et al., 1997; Skare et al., 2001). These results originate from studies in both captive and wild populations. In experiments with captive seals, retinoid concentrations returned to normal when animals were fed with slightly contaminated fish (Brouwer et al., 1989b). Unfortunately, only plasma was analysed, so the mechanisms of this decrease were unclear. Given the homeostatic regulation of retinoid mobilisation, variation in plasma is expected to be lower than in other tissues such as liver or blubber. The only exception (Table 3)
appears to be the study by Simms et al. (2000), which showed that, although retinoid levels in more polluted populations of harbour seal pups were lower than those in a cleaner population, in non-nursing pups levels were positively correlated with organochlorine levels in the blubber. This correlation was explained by the mobilisation of hepatic stores of retinoids into blood and the disruption of the vitamin A transport complex following exposure to milk-derived pollutants, as previously observed in laboratory and terrestrial mammals.


REFERENCES


