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The Influence of Metal Pollution on the Immune System A Potential Stressor for Marine Mammals in the North Sea

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Marine mammals of the North Sea are loaded with metal pollutants. The environmental exposure induces concentrations bioavailable to immune cells high enough to affect their function. Such an imbalance of the immune system caused by pollutants may play a significant role in the incidence of infectious diseases in marine mammals. Metals influence the function of immunocompetent cells by a variety of mechanisms. Depending on the particular metal, its speciation, concentration and bioavailability, and a number of other factors, a continuous metal exposure will result in an immunosuppression or immunoenhancement effects. Both effects were demonstrated on the cellular level in animals of the North Sea. This article reviews metal concentrations in the North and Baltic Seas particularly in tissues of marine mammals, discusses pollutants effects on health and immune functions, and underlines the still existing problem of animals living in polluted coastal areas.

The harbor (or common) seal, *Phoca vitulina*, the grey seal, *Halichoerus grypus* and the harbor porpoise, *Phocoena phocoena* are the most prominent domestic marine mammals in the Wadden Sea. Beside these species several other marine mammals occur in the Wadden Sea and adjacent North Sea as stragglers or regular visitors such as harp seal, *Phoca groenlandica*, hooded seal, *Cystophora cristata*, ringed seal, *Phoca hispida*, bearded seal, *Erignathus barbatus*, walrus, *Odobenus rosmarus*, various species of dolphins as well as large cetaceans, e.g. the minke whale, *Balaenoptera acutorostrata*, and sperm whale, *Physeter macrocephalus*. Seals living in the coastal area are strongly influenced by anthropogenic activities such as fishery, off-shore activities, habitat destruction and environmental pollution.

Since 1978 The Netherlands, Germany and Denmark have been working together on the protection and conservation of the Wadden Sea, which results in the development of the “Trilateral Monitoring and Assessment Program” (TMAP). Within this agreement the seal population is supposed to serve as a bioindicator for the Wadden Sea ecosystem. Seals are considered as indicators for medium and long-term changes in the ecosystem due to their widespread distribution over the coastal areas, their high trophic level, which results in a bioaccumulation and biomagnification of chemicals in their tissues, their long-life span and relatively late maturity including a low reproduction rate. All these factors serve to qualify harbor seals as biomarkers of chemical exposure in the Wadden Sea.

In addition, the “Seal Agreement” has been adopted, which establishes terms of research and monitoring including the monitoring of pollution and investigations on the effects of substances e.g. organochlorine compounds, metals and oil on the seal population. These terms have been specified in the “Seal Management Plan for the Wadden Sea Seal Population” which utilizes parameters such as reproduction, mortality and health status to assess the seal population and includes e.g. immunological, physiological, toxicological, pathohistological and microbiological research.

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The growth of the harbor seal population in the Wadden Sea was interrupted by a phocine distemper virus epizootic in 1988 and 2002. In this context, the influence of pollutants on the immune system has been repeatedly discussed.

Metals in the North and Baltic Seas

In the past, the North Sea ecosystem was highly loaded with both organic and metal pollutants introduced by various anthropogenic activities within the coastal zones. Until the middle of the eighties the yearly input of metal pollution caused by rivers, direct discharge, dumping at sea, atmospheric input and combustion at sea was around 340 tonnes Cd, 75 t Hg, 11.000 t Pb, 5.000 t Cr and 2.150 t Ni (Rachor & Rühl, 1990). A review on the pollution situation in the North Sea has been published by Kersten et al., 1988. Table 1 gives an overview of selected references dealing with environmental research on metals in the North and Baltic Sea.

Current studies have shown a diminishing trend in the input of pollutants into the ecosystem. The BLMP monitoring program (Bund-Länder-Messprogramm) confirmed this general tendency for metal pollutants, however it is necessary to consider this conclusion more detailed. The concentrations of Hg, Cd, Pb and Zn in water and sediment for example are still elevated compared to the “Background Reference Concentrations” which the Convention for the Protection of the Marine Environment of the North-East Atlantic (OSPAR) derived for the “Greater North Sea” (Schmolke et al., 2005).

The Quality Status Report of the TMAP concluded that major reductions in the input and the concentrations of metals in the Wadden Sea occurred mainly in the late 1980s until the early 1990s and continued moderately until 2002. However, local and metal specific elevated concentrations compared to the proposed background values were still frequently investigated (Bakker, van den Heuvel-Greve, & Vethaak, 2005).

Metal body burdens in the mammals of the North and Baltic Seas

Contaminants found in various marine mammal species in the North and Baltic Seas include organochlorine pollutants (Bruhn, Kannan, Petrick, Schulz-Bull, & Duinker, 1999; Hall et al., 1999; Holsbeek et al., 1999; Kleivane, Skaare, Bjorge, Deruiter, & Reijnders, 1995; Sormo, Skaare, Jussi, Jussi, & Jenssen, 2003; Troisi et al., 2000), polybrominated diphenyl ethers (Kalantzi, Hall, Thomas, & Jones, 2005; Law, Allchin, Bennett, Morris, & Rogan, 2002), perfluorinated sulfonates (Kannan et al., 2002; Van de Vijver et al., 2004) and metals (Table 2).

Table 1
Selected studies on metal concentrations in the environment of the North and Baltic Seas.

Object of investigation	Element	Location	Reference
Fish	Cd, Cu, Hg, Pb, Zn	Baltic Sea	Perttilä et al., 1982a
Fish	Cd, Cu, Hg, Pb, Zn	Baltic Sea	Perttilä et al., 1982b
Fish	As	North Sea	Falconer et al., 1983
Water (surface water)	Al, Cd, Co, Cu, Mn, Ni	North Sea	Kremling & Hydes, 1988
Sediments	As, Cd, Cu, Hg, Pb, Zn	North Sea	Chapman, 1992
Fish, Shrimp, Mussel	Hg, Se	North Sea, Belgium	Guns & Vyncke, 1992
Fish, Mussel, Sediments	Ni	Baltic Sea Gdansk Bay	Skwarzec et al., 1994
Sediments	Ag, Al, Ca, Cd, Co, Cr, Cs, Cu, Fe, K, Li, Mg, Mn, Na, Ni, P, Pb, Rb, Sr, Zn	Baltic Sea Gdansk Bay	Szefer et al., 1996
Birds	Cd, Cu, Hg, Se, Zn	North Sea, German Bight	Wenzel et al., 1996
Fish, Birds, Sediments	Organo-Sn	Polish Coast Baltic Sea	Kannan & Falandysz, 1997
Water (dissolved fraction, particulate matter)	Cd, Co, Cu, Fe, Mn, Ni, Pb, Zn	Southern North Sea	Millward et al., 1998
Fish	Hg, Cu	North Sea	Broeg et al., 1999
Sediment	Cd, Cu, Pb, Zn	North Sea, Dutch coastal zone	Laane et al., 1999
Birds	Cd, Cr, Cu, Fe, Ni, Pb, Zn	North Sea, Belgian coast	Debacker et al., 2000
Water	Co, Cu, Fe, Zn	Baltic Sea, Skagerrak	Croot et al., 2002
Sediment, Suspended particulate matter	Al, Fe, K, Mn, Pb	North Sea, German Bight	Hinrichs et al., 2002
Water (coastal water, dissolved)	Co, Cu	Western North Sea	Achterberg et al., 2003
Sediments	Ba, Cd, Cr, Cu, Hg, Ni, Pb, V, Zn	North and Baltic Sea	Breuer et al., 2004
Asteroids, Sediments	Cd, Cu, Pb, Zn	North Sea, Southern Bight	Danis et al., 2004
Water (dissolved fraction, particulate matter, surface & deeper water)	Cd, Cu, Hg, Pb, Zn	Western and Central Baltic Sea	Dippner & Pohl, 2004
Fish	Cd, Cu, Mn, Pb	North Sea, Southern Bight	Henry et al., 2004
Asteroids	Cd, Cu, Pb, Zn	North Sea, Southern Bight	Danis et al., 2006
Mussel	Cd, Cu, Ni, Pb, Zn	German Wadden Sea	Jung et al., 2006
Air, Precipitation	Hg	North Sea Area	Wängberg et al., 2007

Table 2
Summary of studies on metal concentrations in tissues of marine mammals of the North and Baltic Seas.

Species	Organ	Element	Location	Reference
Phocoena phocoena, Lagenorhynchus albirostris	B, L, M	Cu, Hg, Pb, Zn	Denmark	Andersen & Rebsdorff, 1976
Phoca vitulina	Br, K, L	Cd, Cu, Hg, Pb, Zn	German Wadden Sea	Drescher et al., 1977
Phocoena phocoena, Phoca vitulina, Phoca hispida, Halichoerus grypus, Hyperoodon ampullatus, Delphinapterus leucas	K, L, M	Cd, Cu, Hg, Pb, Zn	North and Baltic Coasts, Germany	Harms et al., 1978
Phoca vitulina	B, Br, He, K, L, Pl, Sp	Cd, Cr, Cu, Fe, Mn, Pb, Zn	Dutch Wadden Sea	Duinker et al., 1979
Phoca vitulina	Br, K, L	Br, Hg, Se	Wadden Sea	Reijnders et al., 1980
Phocoena phocoena	Br, K, L,	Cd, Cu, Hg, Pb, Zn	Scotland	Falconer et al., 1983
Phocoena phocoena, Tursiops truncates, Halichoerus grypus, Stenella coeruleoalba	B, L, M	Cd, Cr, Cu, Hg, Ni, Pb, Zn	Irish Sea	Morris et al., 1989
Phoca vitulina	L	As, Cd, Cu, Hg, Se, Zn	Norwegian	Skaare et al., 1990
Phoca vitulina, Halichoerus grypus, Tursiops truncates, Lagenorhynchus albirostris, Lagenorhynchus acutus, Delphinus delphis, Stenella coeruleoalba	L	Cd, Cr, Cu, Hg, Ni, Pb Zn	Waters around British Isles	Law et al., 1991
Phocoena phocoena, Physeter macrocephalus, Delphinus delphis, Tursiops truncatus	K, L, M	Hg	Denmark, Belgium	Joiris et al., 1991
Phoca vitulina, Halichoerus grypus, Phoca hispida	K, L	Al, Ca, Cd, Co, Cr, Cu, Fe, Mg, Mn, Ni, Pb, V, W, Zn	Swedish waters	Frank et al., 1992
Phoca vitulina	H, S	Cd, Hg, Pb	German Wadden Sea	Wenzel et al. 1993
Phocoena phocoena	L	Organo-Sn	Polish Baltic Sea	Kannan & Faladysz, 1997
Phocoena phocoena, Halichoerus grypus	L	Organo-Sn	Waters around British Isles	Law et al., 1998
Physeter macrocephalus	B, K, L, M	Cd, Cr, Cu, Fe, Hg, Ni, Pb, Se, Ti, Zn	Southern North Sea	Holsbeek et al., 1999
Grampus griseus, Lagenorhynchus albirostris, Delphinus delphis, Stenella coeruleoalba, Globicephala melas, Lagenorhyncus acutus, Kogia breviceps, Mesoplodon bidens, Mesoplodon densirostris, Hyperoodon ampullatus, Balaenoptera physalus, Balaenoptera acutorostrata	L	Organo-Sn	Waters around British Isles	Law et al., 1999
Phocoena phocoena, Lagenorhyncus albirostris	K, L, M	Hg	North and Baltic Coasts, Germany	Siebert et al., 1999

Phocoena phocoena	L	Cd, Cr, Cu, Hg, Ni, Pb, Se, Zn	England, Wales	Bennett et al., 2001
Phoca hispida	K, L, M	Cd, Hg, Pb, Se	Baltic Sea, Svalbard	Fant et al., 2001
Grampus griseus, Lagenorhynchus albirostris, Delphinus delphis, Stenella coeruleoalba, Globicephala melas, Lagenorhyncus acutus, Kogia breviceps, Mesoplodon bidens, Balaenoptera physalus, Balaenoptera acutorostrata	L	Ag, As, Cd, Cr, Cu, Fe, Hg, Ni, Pb, Se, Zn	Waters around British Isles	Law et al., 2001
Phocoena phocoena	K, L, K	Cd, Cr, Cu, Fe, Mn, Ni, Pb, Zn	Southern Baltic Sea, Danish and Greenland coastal waters	Szefer et al., 2002
Phocoena phocoena, Phoca vitulina, Phoca hispida	B, Br, K, L, M, S,	organo-Sn	Norwegian	Berge et al., 2004
Phocoena phocoena, Phoca hispida, Halichoerus grypus, Stenella coeruleoalba	L	organo-Sn	Polish Baltic Sea	Ciesielski et al., 2004
Phocoena phocoena	K, L, M	Cd, Cu, Fe, Hg, Se, Zn	Belgium, France, Germany (North and Baltic Sea), Denmark	Das et al., 2004
Phoca vitulina	Bl	Al, As, Be, Cd, Cr, Co, Cu, Au, Fe, Pb, Mn, Mo, Ni, Pd, Pt, Se, Ag, Sn, Ti, Zn	German Wadden Sea	Kakuschke et al., 2005
Phocoena phocoena	L	Hg, organo-Sn	Danish waters	Strand et al., 2005
Phocoena phocoena, Phoca hispida, Halichoerus grypus, Stenella coeruleoalba	L	Al, B, Ba, Ca, Cd, Co, Cr, Cu, Fe, Ga, Hg, K, Li, Mg, Mn, Mo, Na, Ni, P, Pb, Se, Si, Sr, Tl, V, Zn	Polish Baltic Sea	Ciesielski et al., 2006
Phoca vitulina	Bl	Ca, Cu, Fe, K, P, Rb, S, Se, Sr, Zn	German Wadden Sea	Griesel et al., 2006
Halichoerus grypus	Bl	Al, As, Be, Cd, Cr, Co, Cu, Au, Pb, Mn, Mo, Ni, Pd, Pt, Se, Ag, Sn, Ti, V, Zn	German Wadden Sea	Kakuschke et al., 2006
Phocoena phocoena	K, L	Cd, Cu, Hg, Se, Zn	Southern North Sea	Lahaye et al., 2007
Phoca vitulina	Bl	Al, As, Be, Ca, Cd, Cr, Co, Cu, Fe, K, Pb, Mn, Mo, Ni, Pd, Pt, Rb, Se, Sn, Sr, Ti, V, Zn	German Wadden Sea	Griesel et al., 2008
Phoca vitulina	Bl	Al, As, Be, Ca, Cd, Cr, Fe, Pb, Mn, Mo, Ni, Se, Sn, Zn	German Wadden Sea	Kakuschke et al., 2008a
Phoca vitulina	Bl	Al, As, Be, Ca, Cd, Co, Cr, Cu, Fe, K, Mn, Mo, Ni, Pb, Pd, Pt, Rb, Se, Sn, Sr, Zn	German Wadden Sea	Kakuschke et al., 2008b

B=blubber, Bl=blood, Br=brain, M=muscle, L=liver, K=kidney, S=skin, Sp=spleen, He=heart, Pl=placenta, H=hair

Most studies on metal body burdens focused on the investigation of metal concentrations in the liver, kidney or muscle, i.e. tissues available only through post-mortem examination. In living animals the choice of samples is mostly restricted to blood and hair. However, because of sampling difficulties, up to now only few studies have reported values for metals in the blood of marine mammals (Baraj et al., 2001; Caurant & Amiard-Triquet, 1995; Nielsen, Nielsen, Jorgensen, & Grandjean, 2000) and in particular for pinnipeds in the North Sea (Griesel et al., 2006; Kakuschke et al., 2005, 2006). Current studies suggested relatively high metal concentrations in living seals of the North Sea compared to human blood reference values as well as local differences in metal concentrations (Griesel, Kakuschke, Siebert, & Prange, 2008). Furthermore newborn seals in the North Sea showed high body burdens of selected metals, probably caused by a transplacental transfer from the mother to fetus or through the milk during the lactation period (Kakuschke, Griesel, & Prange, 2008a).

Metal pollutants and marine mammal health

Metals and their effects on marine mammals have been reviewed by Das, Debacker, Pillet, & Bouquegneau (2003), O'Shea (1999), and Reijnders, Aguilar, & Donovan, (1999). Nevertheless, apart from metal body burden data, only limited information is available, especially on the related health effects. Hyvärinen & Sipilä (1984) found a relationship between stillbirths of ringed seal (*Pusa hispida saimensis*) pups from Finland and the Ni concentrations in hair samples. Experimental intoxication of harp seal (*Pagophilus groenlandicus*) with methyl-Hg by daily oral intake (25mg/kg) was found to result in lethargy, weight loss and finally death (Ronald, Tessaro, Uthe, Freeman, & Frank, 1977). The corresponding blood parameters indicated renal failure, uremia and toxic hepatitis. Rawson et al. (1993) found an accumulation of lipofuscin in the liver cells of stranded Atlantic bottlenose dolphins (*Tursiops truncatus*) caused by a Hg induced inhibition of the activity of digestive enzymes, which finally results in an increased number of liver diseases. In a case study Shlosberg et al. (1997) described progressive liver damage and finally death of a bottlenose dolphin resulting from Pb intoxication. Studies on the adrenal and testicular steroidogeneses in the grey seal (*Halichoerus grypus*) and harp seals (*Pagophilus groenlandicus)* indicated altered biosyntheses caused by metal contaminants (Freeman, Sangalang, Uthe, & Ronald, 1975; Freeman & Sangalang, 1977). Methyl-Hg intoxicated harp seals showed a low level of damage of sensory cells of the organ of Corti (Ramprashad & Ronald, 1977).

Some researchers have used an indirect approach to investigate the prediction that metal pollutants result in lower resistance to diseases. The endangered population of belugas (*Delphinapterus leucas*) in the polluted estuary of the St. Lawrence River showed high concentrations of organochlorines, heavy metals, and benzo[*a*]pyrene in tissues as well as a high prevalence of tumors which suggests an influence of contaminants through a direct carcinogenic effect and/or a decreased resistance to the development of tumors (De Guise, Lagace, & Beland, 1994). Siebert et al. (1999) investigated Hg body burden and diseases in harbor porpoises (*Phocoena phocoena*) from the German Waters of the North and Baltic Seas. High Hg concentrations were associated with a prevalence of parasitic infections and pneumonia. Bennett et al. (2001) investigated harbor porpoises found dead along the coasts of

England and Wales that died as a consequence of physical trauma as well as infectious diseases. They found that the mean liver concentrations of Hg, Se, the Hg:Se molar ratio and Zn were significantly higher in the porpoises that died of infectious diseases in comparison to those who died because of a physical trauma. Similarly, Kannan, Agusa, Perrotta, Thomas, & Tanabe (2006) and Kannan, Guruge, Thomas, Tanabe, & Giesy (1998) investigated the concentrations of butyl-Sn residues and trace elements in sea otters (*Enhydra lutris nereis*) found dead along the California coastal waters. They studied otters that died due to infectious diseases as well as those that died because of other reasons. Otters that died because of infectious diseases indicated higher concentrations of butyl-Sn in comparison to those that died as a result of physical trauma. The concentrations of Mn, Co, Zn, and Cd were elevated in the diseased and emaciated sea otters relative to the non-diseased sea otters. An elevated accumulation of tributyl-Sn was also found in bottlenose dolphins (*Tursiops truncatus*) stranded along the Atlantic and Gulf coasts of Florida (Kannan et al., 1997). These relationships are substantiated by the fact that the pollution with metals may affect the immunocompetence and disrupt the immune homeostasis of free-ranging populations of marine mammals in many areas of the industrialized world.

Metal influences on immune functions

Metals influence the function of immunocompetent cells by a variety of mechanisms. Depending on the particular metal, its speciation, concentration and bioavailability, and a number of other factors, a continuous metal exposure will result in an immunoenhancement or immunosuppression effects. Reviews of immunomodulation by metals in humans or laboratory animals include those of Chang (1996), Dean, Luster, Munson & Kimber (1994), or Lawrence & McCabe (2002), but metal influences on marine mammals in relation to environmental contamination have been only poorly investigated.

Immune cells such as macrophages can incorporate and store metal components, e.g. Hg and Se in mineral granules, as described for various marine mammal species (Nigro & Leonzio, 1996). In *in vitro* experiments, a similar incorporation of Ti was shown for blood macrophages of harbor seals (Figure 1a). Depending on the concentration, metals can be cytotoxic for immune cells as well as inhibit or stimulate cell functions, the latter in all probability by binding to proteins.

Killer cell activity, phagocytosis and transformation of lymphocytes have been investigated in various marine mammal species and evidence for the immunosuppression function of metal pollutants has been provided. The mitogen-induced proliferation of immune cells was inhibited by butyl-Sn compounds in several marine mammals and humans (Nakata et al., 2002). Phagocytosis and lymphoblast transformation in grey seal pups were adversely affected by Hg *in vitro* (Lalancette, Morin, Measures, & Fournier, 2003). The effects of heavy metals on beluga whale splenocytes and thymocytes *in vitro* indicate functional impairment (De Guise, Bernier, Martineau, Beland, & Fournier, 1996). Pillet et al. (2000) found a sex-dependent effect of Zn on phagocytic activity. In a study on harbor seal pups from the North Sea, lymphocyte proliferation was especially inhibited by Be, Pb, Cd and Hg in newborn pups (Kakuschke et al., 2008c). Interestingly, the susceptibility to the toxic effects of metals seems to be decreased in infant pups.

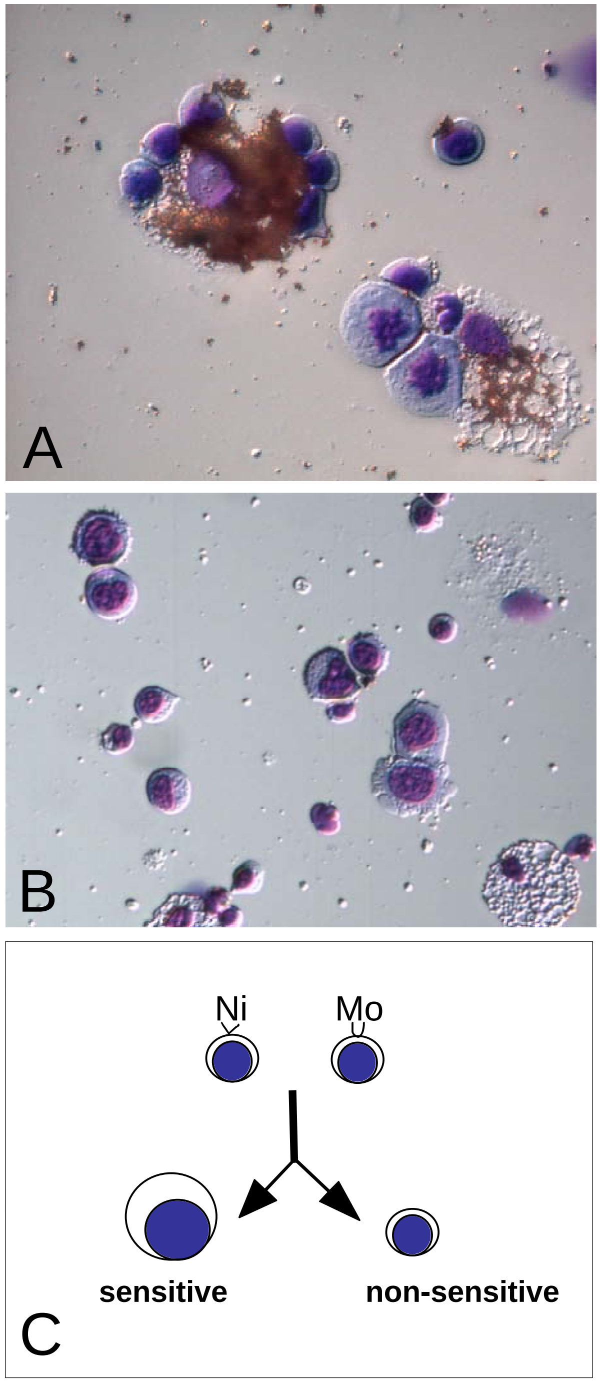

Figure 1. Morphological analysis of Ti-induced (A) and Ni-induced (B) lymphocyte proliferation. In A: two lymphoblasts, one macrophage with ingested titanium particle, and several resting lymphocytes. In B: several lymphoblasts, one macrophage, and resting lymphocytes. C: Principal transformation of lymphocytes.

In addition to immunosuppression, metal pollutants may induce immunoenhancement leading to hypersensitivity and autoimmunity. Even though the metal input into the marine system appears to have been decreasing in recent years, low-level metal concentrations can modulate the immune system. The chronic intake of metal pollutants renders marine mammals candidates for developing hypersensitivity reactions. A lymphocyte transformation test for detecting antigen-specific metal sensitivities according to the MELISA® (memory lymphocyte immuno-stimulation assay) (Stejskal, Cederbrant, Lindvall, & Forsbeck, 1994; Valentine-Thon & Schiwara, 2003; Valentine-Thon, Sandkamp, Müller, Guzzi, & Hartmann, 2005) was used to investigate pinnipeds from the North Sea (Kakuschke et al., 2005, 2006). The method is based on the fact that lymphocytes, which have been sensitized by a certain metal ("memory cells"), transform into blasts and proliferate when they are re-exposed to this metal (Figure 1). Altogether 31 pinnipeds from the North Sea were investigated, including 13 pups and 17 adult harbor seals as well as one grey seal (Kakuschke, 2006). 13 of these 31 animals showed such a metal-specific delayed type hypersensitivity reaction. The frequency of sensitizing metals was in the order Mo > Ni > Ti > Cr, Al > Pb, Be, Sn. Furthermore, a relationship between the blood levels of metals and this immunological dysfunction was reported (Kakuschke et al., 2005).

In the case study of the grey seal the hypersensitivity reaction to Ni and Be could be validated by different approaches – the proliferation of memory lymphocytes as well as the altered cytokine pattern (Kakuschke et al., 2006). With the cytokines interleukin-2 (IL-2) and interleukin-4 (IL-4) it is possible to distinguish between T-helper 1 (Th1), IL-2 secreting cells and T-helper 2 (Th2), IL-4 producing cells (Elenkov & Chrousos, 1999). The impact of stress on the cytokine pattern was recently described for harbor porpoises from the North Sea (Fonfara, Siebert, Prange, & Colijn, 2007). Kakuschke et al. (2006) measured the mRNA-expression of IL-2 and IL-4 in grey seal lymphocytes co-cultivated with the sensitizing metals Ni and Be as well as the non-sensitizing metals Hg and Cd. Ni and Be induced the lowest cytokine expression compared to the other metals and the quotient IL2/IL4 was increased due to a strong down-regulation of the Th2 cytokine IL-4, which suggests an antigen-specific delayed-type hypersensitivity reaction with a Th1/Th2 polarization toward Th1 (Kidd 2003).

Summary

The environmental exposure with metals is believed to affect marine mammal health adversely. One mechanism whereby metals can alter the health status is through modulation of immune homeostasis. Metals may change the response repertoire by direct and indirect means, which include changes in cell proliferation, phagocytosis, protein expression or other cell functions. Some resulting effects may include immunosuppression or acute as well as chronic inflammatory processes leading to hypersensitivities or autoimmune diseases. The multiple influences of metals on the immune system underline the importance of metals pollution as a potential stressor for marine mammals.

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