

Interactions and Potential Causes to the M74 Syndrome Affecting Sea-Run Baltic Salmon (*Salmo salar*) Populations

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Baltic salmon (*Salmo salar*) populations originating from the Swedish East Coast have suffered from the reproduction disorder M74 since 1974. Between 1992–96 the mean frequency of M74 in Swedish compensatory rearing stations varied between 50 and 80%. The highest recorded incidence of M74 was in 1993 when 96% of all family groups from the River Ume developed M74. Since 1997 the mean annual frequency of M74 in Swedish compensatory rearing stations has been about 25%. Finnish and Estonian Baltic salmon have also demonstrated development of M74 in the 1990s. Several factors have been hypothesized to be involved in the aetiology including loading of man-made pollutants, lowered levels of antioxidant compounds and large-scale changes of the food web with accompanying alterations of the nutritional quality of the basic prey species for Baltic salmon (Norrgren et al. 1993a; Börjeson and Norrgren 1997). However, today it is evident that the primary cause of M74 is a deficiency in thiamine (Vitamin B₁) due to a poor maternal transfer (Amcoff et al. 1998a). M74-similar syndromes (EMS and Cayuga Syndrome) also affect several salmonid species in the North American Great Lakes (Fisher et al. 1995; Fitzsimons 1995; Marcquenski and Brown 1997). Thiamine is essential as a co-factor for three enzymes necessary in carbohydrate metabolism: the transketolase in the non-oxidative part of the pentose phosphate shunt; the pyruvate dehydrogenase complex in the junction between the glycolytic pathway and the citric acid cycle; and the α -ketoglutarate dehydrogenase complex in the citric acid cycle. The pentose phosphate shunt produces NADPH and ribose 5-phosphate, compounds necessary in reductive biosynthesis and for DNA ribonucleotides. Lowered thiamine content results in lowered activities of the thiamine dependent enzymes, which is considered to be the initial event in the development of clinical signs. Thiamine deficiencies have been shown to cause a variety of neuropathologies with lethal outcome in many different animals including humans (Evans 1975). In fish, typical symptoms are anorexia, instability, convulsions and darkening of the skin (Blaxter et al. 1974; Lehmitz and Spannhof 1977; Morito et al. 1986; Masumoto et al. 1987; Lundström et al. 1998a). Biochemical changes include accumulation of lactic acid, depletion of hepatic and muscular glycogen depots and altered activities of brain transmitter substances (Amcoff et al. in press a). Brain areas with extensive single cell necrosis are commonly found in M74-developing yolk-sac fry (Lundström et al. 1999a). The M74 syndrome is usually regarded as a yolk-sac fry thiamine deficiency with the progeny demonstrating M74-typical neurological disturbances followed by death prior to swim-up. Development of disease is predetermined by the maternally transferred concentration of thiamine to the offspring and yolk-sac fry with a thiamine content below the threshold limit interval of 0.34–0.47 nmol/g have lowered thiamine-dependent enzyme activities and will develop M74 (Amcoff et al. 1998b, 2000). Data show that offspring with thiamine levels just above the threshold limit interval have restrained enzyme activities, indicating that seemingly healthy Baltic salmon yolk-sac fry suffer from a sub-lethal thiamine deficiency (Amcoff et al. 2000). Thiamine deficiencies during early development in the rat reduce the activities and alter the cerebral distribution pattern of the thiamine-dependent enzyme, possibly due to tissue-selective vulnerability (Sheu et al. 1996). Whether sub-lethal thiamine deficiencies affect future performance in Baltic salmon is not known. By using thiamine antagonists that specifically bind to the thiamine-dependent enzymes most of the typical M74-symptoms may be reproduced (Amcoff et al. 1999, in press a). The M74-syndrome is female dependent, however, in severe cases adult salmon of both sexes develop thiamine deficiency and die before spawning. These fish manifest a typical in-coordinative behavior and have problems with the regulation of their swim-bladder pressure (Amcoff et al. 1998a). In addition, they have altered brain serotonergic and dopaminergic activities, possibly contributing to the aberrant behavior (Amcoff et al. in press b). Both adult fish and their offspring can be treated to full survival with thiamine treatments (Amcoff et al. 1998b).

The Baltic Sea ecosystem is a contaminated environment and it has been suggested that the M74-syndrome is caused by maternal transfer of different organohalogen substances to the oocytes (Norrgrén et al. 1993a). Studies on mammals show that exposure to polychlorinated biphenyls (PCBs) and dichloro-diphenyltrichloroethane (DDT) may give rise to a thiamine deficiency (Yagi et al. 1979; Pélissier et al. 1992). Asplund et al. (1999) and Vuorinen et al. (1997) showed that Baltic salmon tissues and eggs contain high levels of organohalogen compounds, though no clear connection with M74 development was found. Experimental studies to induce M74 have been performed by exposures to model substances like PCBs, polychlorinated naphthalenes (PCNs) and extracts from sediments and animal tissues (Norrgrén et al. 1993b; Engwall et al. 1994; Holm et al. 1994; Amcoff et al. 1998c; Lundström et al. 1998b). However, none of these studies succeeded in inducing M74.

A common effect of organohalogen biotransformation is free radical generation with an accompanying consumption of free radical scavengers in addition to induced biotransformation systems (Halliwell and Gutteridge 1996). M74-developing yolk-sac fry have reduced concentrations of ascorbic acid, α -tocopherol and ubiquinone, three of the most important antioxidant vitamins (Börjeson and Norrgrén 1997). They also demonstrate altered activities of catalase, glutathion reductase, glutathion peroxidase and cytochrome P4501A, indicating that organohalogens may play a role in further worsening the situation for individuals with low thiamine content being on the edge of survival (Amcoff et al. 1999; Lundström et al. 1999b; Amcoff et al. 2000, in press a).

The cause of the low thiamine levels found in Baltic salmon is not completely resolved. A study by Karlsson et al (1999) showed that Baltic salmon have not changed their preference for herring (*Clupea harengus*) and sprat (*Sprattus sprattus*) since the early 1960s, indicating that factors other than food choice have to be addressed. One factor that is of great interest is the presence and regulation of thiaminase, a thiamine-destroying enzyme present in herring and sprat.

In conclusion, the M74 syndrome is primarily caused by a maternally transferred thiamine deficiency from the female to the oocytes. The exact causes of the deficiency are not known. M74 still constitutes a severe threat to the survival of the remaining self-sustaining Baltic salmon populations.

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