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Wpływ heksachloronaftalenu (HxCN) na wybrane wskaźniki toksyczności podprzewlekłej u samic szczura

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Summary

The effects of subchronic administration of hexachloronaphthalene (HxCN) on selected parameters of systemic toxicity in female Wistar rats

The dissertation addresses the toxicity of polychlorinated naphthalenes (PCNs) – compounds that were included in 2015 into the persistent organic pollutants (POPs) under the Stockholm Convention. Chemicals included in POPs have been considered for many years the most dangerous environmental poisons for humans. Due to high, unpredictable risk of adverse effects on human health, including reproductive effects, embryotoxicity, teratogenicity, genotoxic and carcinogenic effects, POPs have been recognized as particularly dangerous xenobiotics, for which it is recommended to perform comprehensive toxicological tests.

Mixtures of PCNs were very widely used in many industries, among others, as dielectrics, refrigerants, extinguishing agents and flame-retardants until the end of the 1980s. Due to their very high persistence, bioaccumulation and biomagnification, they have become global environmental pollutants. For this reason, restrictions on their use and production have been introduced. Currently, waste incineration and household furnace emissions are considered the main sources of environmental pollution of PCNs, in addition to the technical preparations produced in the past.

Hexachloronaphthalene (HxCN) is considered one of the most toxic congeners of PCNs. However, little is known about toxicity of this compound, which is commonly detected in human adipose tissue and organs (mainly in the liver) around the world because of its ubiquity in the environment worldwide.

The aim of this doctoral thesis was to make the first assessment of the toxicity of hexachloronaphthalene (HxCN) administered to female Wistar rats for 90 days. HxCN was synthesized and its purity was over 95%. The research was approved by the Local Ethics Committee for Experiments on Animals (Resolution No. 13 / ŁB703 / 2014).

In the first stage, a preliminary study (short-term toxicity) was carried out to determine the level of doses for the main study (subchronic toxicity – second stage). In both cases, virtually the same parameters and biochemical indicators were taken into account. Systemic effects – integral toxicity indicators, i.e. daily clinical observations, control of food and water intake, body weight gain, relative and absolute organ weights, hematological parameters, liver damage indicatory enzymes, parameters assessing renal function, selected parameters of oxidative stress in the liver and kidneys and total antioxidant status in the blood as well as the induction of selected cytochromes (CYP1A, CYP2B) in the liver and kidneys were measured.

The study evaluated also the potentially porphyrogenic effect of HxCN covering selected parameters of the heme biosynthesis pathway in the liver, porphyrins profile in the urine and liver as well as the urine level of delta-aminolevulinic acid (ALA). The histopathological examination of selected organs (liver, kidneys, lungs, spleen, thymus, heart, thyroid, adrenal glands, ovaries, uterus, brain, sciatic nerve) was also performed as well as the initial genotoxicity evaluation (micronucleus test) in the bone marrow.

The results of the study show that HxCN induced a dose-dependent, very strong induction of microsomal enzymes, especially CYP1A (more than 100-fold), which is typical of dioxin-like compounds, and CYP2B (more than 3-fold). The liver is the target organ of HxCN long-term toxicity. The hepatotoxicity was expressed as hepatomegaly, increased lipid peroxidation and steatosis. After administration of HxCN in female rats, statistically significant thrombocytopenia and decreased thymic weight was also observed. It has been shown for the first time that HxCN has porphyrogenic potential. Significant inhibition of two key enzymes of the heme biosynthetic pathway in the liver, i.e. delta-aminolevulinic acid dehydratase and uroporphyrinogen decarboxylase was noticed. Changes in concentrations of porphyrins and in their profile in the liver and urine seem to confirm the disorders of the heme biosynthesis. The most spectacular effect of exposure to HxCN was a significant accumulation of uroporphyrins in the liver (so-called hepatic uroporphyria). In animals exposed to the two highest doses of HxCN, a dose-dependent (from 3 to almost 6-fold) increase in the concentration of uroporphyrins in the liver was demonstrated. The consequence of impaired heme biosynthesis in the liver was also changed profile in the excretion of heme precursors in the urine and significantly increased urine ALA levels. The results of the micronucleus test suggest that HxCN is probably not a genotoxic agent in female rats.

The results of this study provide a comprehensive/extensive knowledge on long-term toxicity of HxCN, a representative of PCNs, currently constitutes a significant environmental threat. The lowest adverse effects level – LOAEL of 0.03 mg/kg body weight, derived from the study, can be practically used to assess the health risk for the general population.