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ACRYLAMIDE TOXICITY

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The mankind in the contact with the external environment is all the time exposed to huge amount of different pollutions. Conventionally it concerns atmosphere, watercourses, land, industries and foodstuffs. In the last years attention was devoted to the toxic action of acrylamide. As an important industrial chemical acrylamide (AA) and its polymers are used for floculants of waste waters, production of paper and pulp and for preparation of gels applied in chromatography and electrophoresis.

Acrylamide C_3H_5NO (CAS No 79-06-01) is a colorless and odorless crystalline solid soluble in water. As a monomer it is formed in heated starchy food as a result of Maillard reaction (40, 48). AA is a type – 2 alkene a chemical class that includes structurally related electrophilic environmental pollutants and endogenous mediators of cellular oxidative stress (35). Chromatographic methods enable fast, accurate and reproducible determination of AA (3, 52). AA is metabolized primarily to glycidamide. It also undergoes detoxification by conjugation with glutathione (34). Decomposition products of AA may participate on its toxicity (27, 29, 51). There were assest values of LD_{50} of AA and its derivatives in experimental animals (70). Hemoglobine adducts of AA and glycidamide have been measured as a biomarkers of AA exposure in a represenatative sample of the USA population. Smoking was significantly correlated with these adducts (4, 69). AA is present in commonly used foods (31). Amount of AA in different products are published (34, 48). AA content in dry foodstuffs for dog and cat are also determined (68). Dietary intake of AA differs greatly among European adults residing in different geographical regions (18). Poland young population consumes the highest amount of AA (73). Specially the AA content in baby food products is even dozen times higher than the exposure estimated for the total Polish population (40).

Neurotoxic effects of AA were proven in laboratory animals in vivo and in vitro. They ivolve the peripheral and the central nervous system by the damage of the nerve ternimals through membrane fusion mechanisms and tubulovesicular alterations. Changes in neural specific $mRNA_s$ are sensitive to neurotoxic damage (67). In cultured fibroblast cell lines AA is responsible for neurite disintegration (71). Similar effects are with rat dorsal root ganglia (63). There are alterations in the axonal transport of proteins, glycoproteins and

gangliosides in sensory neurons of rat sciatic nerve (24), inhibition of creatine kinase from brain or sciatic nerve (37). Reduction of protein delivery contributes to axonal degeneration (57). Progressive deficits in retrograde axon transport precede degeneration of motor axons (41). There are extensive pathological changes at the neuromuscular junctions (13) and heteregenous visceral nerve changes (17). Axonal atrophy can masc the development of neurofilamentous axonal swelling (21). The incubation of AA with rat brain homogenates was followed by a decrease in catalase activity (65). Changes in the phosphorylation of phospholipids and protein in the nerves are the component of AA neurotoxic mechanism (5). Voltage clamp and electronmicroscopic analysis of rat sciatic nerve confirmed distal axon degeneration (8). Well documented is neurotoxicant effect due to cerebellar Purkinje cell damage and central-peripheral distal axonopathy. In rats the damage of far-field somatosensory evoked potentials may occure through the system including the spinal cord, dorsal column nuclei, medial lemniscus, thalamus and sensory radiation (7). Neuropathy involving sensitive nerves of the rat urinary bladder leads to severe urinary retention (1). Neuropathy in dogs abolished the cough reflex (25). In cats were described spinal cord deffects and peripheral neuropathy (22), in monkeys loss of vibration sensitivity (38), loss of regulation in axoplazma of myelinated rat tibial nerve fibers (35). There is also inhibition of rat mitochondrial energy production (39). Russom et al. (53) describe acute toxicity and behavioral effects of acrylates in juvenile fathead minnows.

AA produces developmental and postnatal effects in mouse and rat offsprings following administration to pregnant dams. It also produces neurotoxic effects in the neonates at levels that are not toxic to the dam. Chromosomal changes indicate its clastogenic potential and genotoxic effects (9, 11). Lower fertilizing ability of the sperm plays a major role in the reduced reproductive competence in rats (62). The same effect has in mice the decrease sperm count and abnormal sperm morphology (55). Mammalian spot test revealed mutagenic and teratogenic effects (42).

Animal experiments provide evidence that AA induces not only mutagenecity but especially mammary gland tumors in female rats (35). Many other tumors were observed, e. g. adenocarcinoma of different organs, papiloma and carcinoma of oral cavity, mesothelioma, pituitary adenoma and adenocarcinoma (12). In a chronic study with AA in drinking water various tumors were found as astrocytoma, oligodendroglioma of the brain, pheochromocytoma of the adrenal gland, malignant leukemia (26) and abberations in the bone marrow (11). In the contact with the skin AA produces in mice irritation, scabbing, hyperceratosis, papillomas, carcinomas and melanomas (72).

The consequences of AA contact in human are not uniform. Association between chemical exposure and selfreported symptoms should be interpreted with great caution, because in tunnel workers previously exposed to grout containing AA there were not found health outcomes as measured by the chosen neuropsychological tests (20). Contrary occupational health hazard in profesional exposition to AA is generally accepted (19). For the most part there are described variable objective unfavourable consequences. Prevail peripheral neuropathies with paresthesia, pain, cramps, attacs of white fingers, hands and

feet accompanied with sweating, numbness and fatigue (50), neurovegetative and neurotic disturbances (30), emesis and diarrhea (70). Often occure allergic contact dermatoses and occupational asthma (28) connected with generalized urticaria in laboratory workers. There are also midbrain, cerebellar and optic nerve alterations. EEG changes were described in workers exposed to AA in laboratory and semibusiness conditions (55). Due to nerve terminal damage AA may contribute to the development of Alzheimer disease (51). Exposure to acrylnitrite was followed by accumulation of acrylate adducts with erythrocytic hemoglobin (4, 65). In a prospective European mother-child study both AA and glycidamide hemoglobin adducts were associated with significant lowering in birth weight and head circumference. Thus dietary intake of AA should be reduced among pregnant women (46). Also the Norwegian mother and child cohort study proved that AA intake during pregnancy was negatively associated with fetal growth (15).

In human there is lack of an increased risk of most types of cancers from exposure to AA. The main association that reqieres further monitoring involves kidney cancer (49). In a prospective study from 10 European countries the dietary intake of AA was not associated with an increased risk of the pankreas adenocarcinoma (44). Also no association was observed between AA intake and endometrial cancer. However a positive association with type I was observed in women who were nonusers of oral contraceptives and never smokers (43). A cohort of 2293 man from the USA and the Netherlands exposed to AA showed no trend of increased risk of mortality from several cancer sites (10). The mortality of 371 employes did not support a cause effect relation between exposure to AA and overal mortality, total malignant neoplasms or any specific cancers (58). Contrary in a Danish cohort of postmenopausal women the prediagnostic exposure to AA was related to mortality of endocrine related types of breast cancer patients (45).

There are efforts to elaborate strategies for mitigation of unfavourable effects of AA. Preventive measures are based on the use of the asparaginase and thermal imput reduction and vakuum treatment aimed to remove the already formed AA from the product (2). There are procedures to reduce AA in the main foods (48). Some dietary components as tea polyphenols in green tea, resveratol in grapes, diallyltrisulfide in garlic, flavonoids in citrus and tomato are able to ameliorate AA toxicity (51). The negative impact of AA on structure and innervation of the small intestine wall in mice can be abolisheed by dietary potato fiber preparations (14). Selenium dietary supplement can prevant the biochemical changes in the liver in rats (66). Fish oil has a neuroprotective effect on the AA induced neurotoxicity in rats (32). Treatment with gangliosides stimulates the regenerative potential of AA damaged nerves (61). ACTH and related peptides improve recovery from neuropathy in rats (60).

SUMMARY

In a review there are described toxic consequences of acrylates in animal experiments, and in man in industry business, in laboratories and in foodstuffs.

Toxicita akrylamidu

SOUHRN

V přehledu jsou popsány toxické účinky akrylátů v pokusech na zvířatech a u lidí v průmyslových provozech, v laboratořích a v potravinách.

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