ABSTRACT

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Title of diploma thesis: Toxicity study of newly developed anthelmintics

One of the problems of current veterinary medicine is the frequent occurrence of diseases caused by parasitic helminths. Treatment often relies solely on the use of currently available drugs, which however develop resistance after a certain period of time. Currently available drugs are often no longer sufficient in therapy, and therefore continuous research and development of new agents is important. In addition to the appropriate mechanism of action and the establishing of efficacy against helminths that are already resistant to current drugs, it is important during development to consider the safety of the compounds for the host organism. Therefore, one of the important phases in the development of new drugs is to prove their safety. To do this, toxicity studies using *in vitro*, *ex vivo* and even *in vivo* methods are still an indispensable part of these studies.

This thesis deals specifically with toxicity studies of two newly synthesized compounds OMK207 and OMK211, which have already been shown to be effective against nematodes. For this testing, both an *ex vivo* model, where precision-cut mouse liver slices were used, and an *in vivo* model, where the test compounds were administered to the ICR mouse strain for LD50 determination, were chosen. In the *ex vivo* testing on liver slices, the substances were tested up to a concentration of 100 μM, which was the limit of solubility. Toxicity assessment was performed by measuring ATP levels in the slices. None of the compounds tested were shown to have a statistically significant effect on the viability of these slices. During *in vivo* testing, the LD50 for our compounds was tested to see if it exceeded 2000 mg/kg b. w. At the same time, the effect of these compounds on the behaviour and weight of the subjects was monitored during the 14 days after administration because of possible manifestations of pathological changes. As all individuals survived after administration of the substances, the LD50 for both compounds exceeds 2000 mg/kg b. w., which is several times higher than some currently used drugs. Regarding the behaviour of the mice after the administration of the compounds, signs of apathy

were observed in the first days, but this gradually disappeared in all the tested animals. In addition, two mice showed necrosis of the tail tip with OMK207, but no other signs of pathology were observed. In one individual, histological analysis of OMK211 revealed changes in kidney cells, but no confirmed causal connection with the drug. Neither compound was found to be highly toxic in the tests performed and both substances appear to be safe for further testing in the target host organism.