DEVELOPMENT OF AN ADVERSE OUTCOME PATHWAY FOR "THYROPEROXIDASE AND/OR DEIODINASE INHIBITION LEADING TO IMPAIRED SWIM BLADDER INFLATION"

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The vast number of industrially produced chemicals has – in the light of the 3R principle – generated a strong focus on alternative test development for ecological risk assessment. Therefore, we are developing a non-animal testing strategy for the prediction of chronic aquatic toxicity including *in vitro* tests and *in vivo* ZFET (zebrafish embryo acute toxicity test, OECD TG 236) assays. Moreover, we are assessing the feasibility of using an adverse outcome pathway (AOP)-based approach for this purpose.

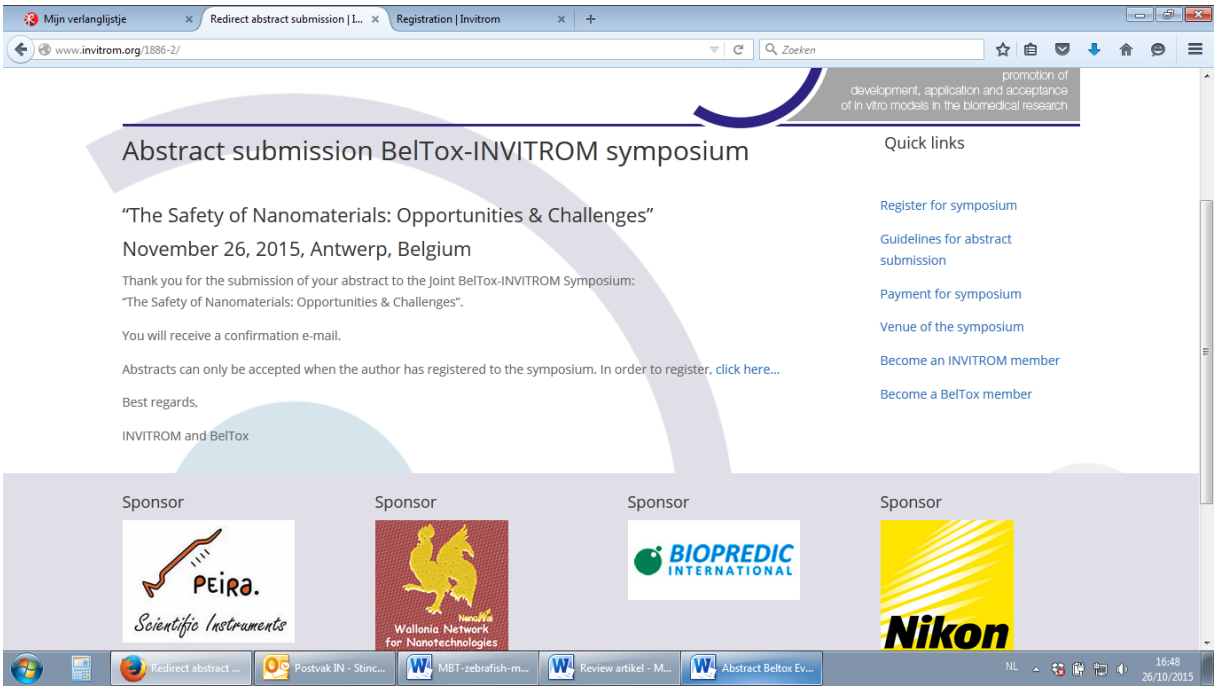
Thyroid hormone (TH) disruption is increasingly recognized as an important mode of action and a major regulatory concern as well. However, endocrine properties of chemicals are often not well-known. Therefore, we are developing an AOP related to TH synthesis and activation, encompassing thyroperoxidase (TPO) and/or deiodinase (DIO) inhibition, impacting swim bladder development and inflation. Impaired swim bladder inflation is considered an ecologically relevant adverse outcome as it affects endpoints including feeding behaviour and predator avoidance, resulting in lower survival probability.

A hypothesized AOP was developed over several iterations using refined 120 hours post fertilization (hpf) ZFET tests, exposing zebrafish embryos to mercaptobenzothiazole (MBT), methimazole (MMI), propylthiouracil (PTU), and iopanoic acid (IOP). Results show that exposure to MBT and MMI, two TPO inhibitors, do not directly impair posterior chamber inflation at 120 hpf, while IOP, a DIO inhibitor, and PTU, which inhibits TPO and DIO, do. Since the posterior chamber inflates during early development, we hypothesized that embryonic TPO activity is not essential for posterior chamber inflation because of the presence of maternal T4 (prohormone), while deiodinase activity is needed to activate T4 into the biologically active T3. Furthermore, we hypothesized that both TPO and DIO are needed to synthesize and activate THs at later developmental stages, since maternally derived THs are depleted and cannot offset TPO inhibition. Subsequently, both TPO and DIO inhibitors were predicted to impair anterior chamber inflation, which occurs during late development.

To investigate this hypothesis, a fish early-life stage toxicity test (FELS, OECD TG 210) was performed, exposing zebrafish embryos to MBT until 32 days post fertilization (dpf). MBT exposure resulted in impaired anterior chamber inflation at 21 dpf, in line with the hypothesized AOP. Furthermore, a clear relationship between T4 levels and anterior chamber surface was found, suggesting that anterior chamber inflation is influenced by THs.

Finally, we investigated the potential of several compounds to inhibit TPO and/or DIO at the enzyme level. The results will be used to (1) investigate a correlation between the TPO/DIO inhibitory potential of compounds and acute and chronic data, (2) build a model to predict swim bladder inflation and (3) validate the impact on swim bladder inflation using ZFET and FELS tests.

Keywords: Adverse outcome pathway; thyroid hormone; swim bladder inflation; zebrafish embryo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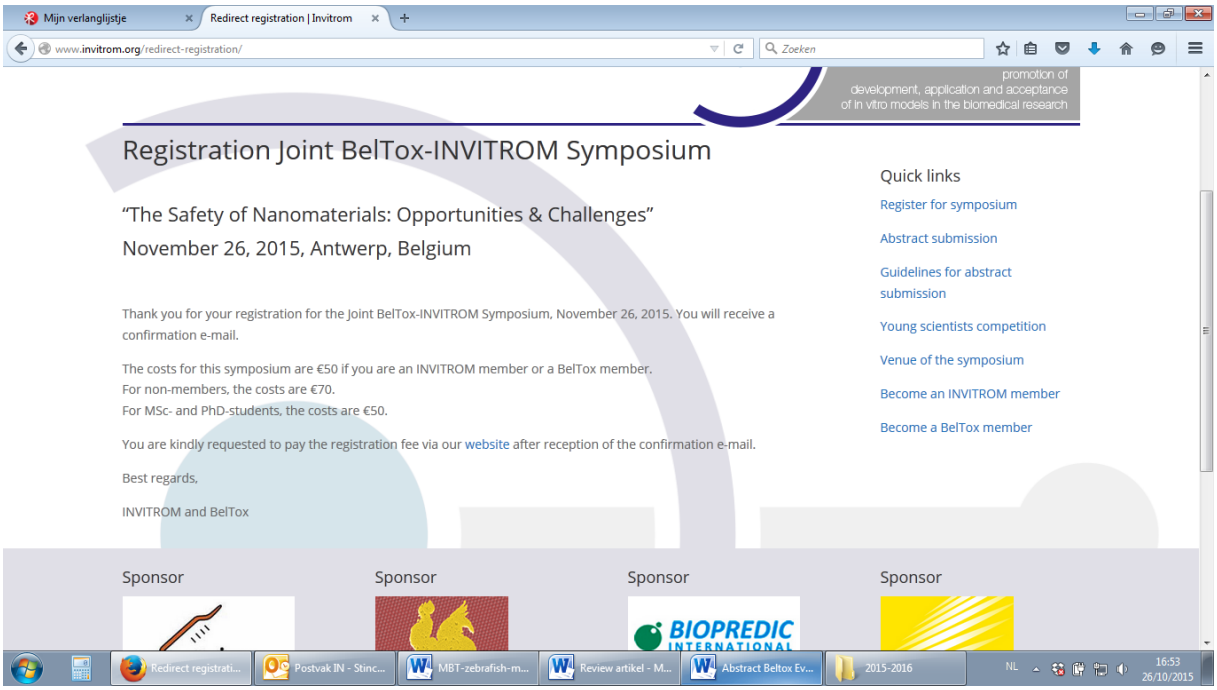
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