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Using In Vitro Testing for A Read-Across Case Study, Compare the Toxicological Effects and Exposure Levels of Triclosan and its Structurally Related Compounds

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Abstract

A possible alternate approach for determining systemic toxicity is likely to be read-across based on structural and biological similarities. Stacking case studies and gleaning important points from them would be a practical technique for quantitative chemical risk assessment. Thus, by contrasting the toxicological consequences based on bad outcome pathways and exposure levels of various structurally comparable compounds for a target organ, we produced a read-across case study. We focused on the hepatotoxicity of triclosan, diclosan, and 1-chloro-3-(4-chlorophenoxy)benzene, which share structural similarities with triclosan. According to the findings of in vitro toxicogenomics, both triclosan and diclosan were frequently found to cause abnormalities in cholesterol production. Both triclosan and diclosan treatment led to equal reductions in hepatocellular cholesterol levels. Furthermore, the liver's exposure to diclosan and triclosan was comparable. These findings demonstrate that the toxicological effects and degree of hepatotoxicity of triclosan and diclosan are comparable. Our prediction results about the toxicological effect and its severity are credible in light of the available repeated dose toxicity data. The current study thus illustrated the applicability of read-across comparison of toxicological effects and exposure levels for quantitative chemical risk assessment.

Keywords: Triclosan; Hepatotoxicity; Quantitative chemical risk assessment; Toxicogenomics

Introduction

In the regulatory context, it is essential to undertake a chemical risk assessment of systemic toxicity prior to employing chemicals in order to safeguard human health (European Chemicals Agency, 2016). Repeated dose toxicity tests, such as those recommended in the OEC guidelines 408 and 409, have been carried out to evaluate systemic toxicity; however, taking into account animal welfare and regulatory constraints, these animal tests should be replaced with non-animal assessment methods. As a result, it's essential to create a promising alternative assessment technique for systemic toxicity that complies with legal requirements [1].

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Materials and Method

Materials

Table 1 summarises general information and data on repeated dose toxicity. The test chemicals were purchased from the following businesses: 1-chloro-3-(4-chlorophenoxy)benzene, AmBeed, Chicago, IL, USA; triclosan, Fuji Film Wako Pure Chemical Corporation, Osaka, Japan; diclosan, Toronto Research Chemicals, Toronto, Canada. In dimethyl sulfoxide, all compounds were dissolved (Fuji Film Wako Pure Chemical Corporation). We utilised the ChemMine Tools to compare structural similarity using the maximum common substructure (MCS) Tanimoto coefficient. According to the findings of earlier investigations, we selected the MCS Tanimoto coefficient >0.7 in this study as a guideline for choosing structurally related compounds.

SD rat Sprague Dawley primary hepatocytes

Each in vitro experiment used primary hepatocytes from male SD rats that had been cryopreserved. The supplier's hepatocytes were extracted in accordance with ARRIVE guidelines and European rules in all animal trials. The provider was given permission to isolate the cells by the institutional ethics committee that approved the supplier's use of animals in its research. The cells were grown in the provided medium at 37 °C with 5% CO_2 (Kurabo, Osaka, Japan). After a 24-hour pre-culture, each chemical was introduced to the group [3, 4].

Processing and analysis of microarray data

The miRNeasy kit (Qiagen, Hilden, Germany) was used to extract total RNA from SD rat primary hepatocytes that had been exposed to each chemical at 30 M for 24 hours in accordance with the manufacturer's recommendations. Thermo Fisher Scientific's NanoDrop One spectrophotometer was used to calculate the final RNA concentration and purity, which resulted in an average RNA concentration of 4 ng/L and purity values of A260/280 1.8 and A260/230 1.5 for all the samples. 100 ng of total RNA was transformed

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into cDNA. Following that, the Low Input Quick Amp Labeling kit was utilised to create cRNA using cDNA (Agilent Technologies, Palo Alto, CA, USA). Labeled cRNA was applied to an Agilent Technologies SurePrint G3 GE 8 60K Ver 2.0 Microarray, which was rotated at 10 rpm for 17 hours at 65 °C. The accession number GSE186659 may be found in the Gene Expression Omnibus database, which can be accessed. In order to analyse microarray data, Genespring GX 14.5 was used (Agilent Technologies). The selection criteria for genes that were significantly up- or down-regulated were the same as in our earlier investigations. The IPA software (Qiagen) was used to determine the canonical biological pathways connected to these genes and their fold variations, with a p-value of less than 0.001[5].

Simulation of liver exposure amount and plasma concentration in silico

Based on the findings of the metabolic activity and cell permeability studies, triclosan and diclosan physiologically based pharmacokinetic (PBPK) modelling and simulation were built using GastroPlus. 3.80 M of triclosan was given during an in vivo pharmacokinetic test in a previous study. In the first step, we compared the simulation results with the pre-existing in vivo pharmacokinetic data at the same concentration of triclosan to verify the accuracy of our PBPK model. As a success criterion for creating a viable PBPK model for triclosan, we employed within three-fold predictions of maximum concentration (Cmax), area under the curve (AUC), and time to maximum concentration (Tmax) in this investigation. The pharmacokinetic parameters for diclosan were then optimised using the PBPK model's framework. We used proven PBPK models to simulate the exposure levels of triclosan and diclosan for the liver at 3.80 mol in order to compare the exposure level at the same concentration. Furthermore, based on earlier repeated dosage toxicity experiments, triclosan did not exhibit hepatotoxicity at 100 mg/kg while diclosan did at this dose. Therefore, we also predicted the exposure levels of triclosan and diclosan for the liver at 100 mg/kg using proven PBPK models in order to examine and confirm the exposure levels at this provided dose using repeated dose toxicity test [6, 7].

Discussion

In the current study, we anticipated PoD by comparing biological and structural similarities for read-cross for triclosan and other structurally comparable drugs in order to acquire crucial considerations and fresh insights for creating new alternative tactics for systemic toxicity. In the past, we demonstrated the value of in vitro toxicogenomics and associated biochemical assays for classifying the substances. The in vitro toxicogenomics was carried out in accordance with the method suggested herein for categorising substances based on the probable pathways for the liver. The biological reactions between triclosan and diclosan demonstrated similar biological responses, including disruption of cholesterol production. After that, we looked into and contrasted how these chemicals affected the production of cholesterol by evaluating the cholesterol levels of primary hepatocytes from SD rat, which had been exposed to each chemical. According to the research, both triclosan and diclosan were equally effective in lowering cholesterol levels in treated cells. Therefore, we deduced that triclosan and diclosan may have comparable toxicological effects on the liver. In a subsequent phase, we used in silico modelling to predict, based on the outcomes of in vitro testing, the exposure level of triclosan and diclosan in the liver. The predicted outcomes demonstrated that the liver was exposed to triclosan and diclosan at comparable levels when the concentration and dose were the same. This prediction may make sense from the perspective of PoD based on the available in vivo data. Consequently, the current read-across case study gives a prototype of a different method of determining systemic toxicity by contrasting Therefore, the current read-across case study compares biological and structural similarities for read-across and gives a prototype of a different assessment technique for systemic toxicity [8].

We performed a microarray study on primary rat hepatocytes from SD rats in order to extract and contrast the likely cause of hepatotoxicity in this group. Microarray analysis, as previously reported, encourages the selection of relevant in vitro tests for categorising the compounds based on their potential mode of action. Based on similar probable processes, such as disturbance of cholesterol synthesis, the data gathered here suggested that triclosan and diclosan were grouped together. As a precursor of bile acid and as a component of the cell membrane, cholesterol is crucial for maintaining cells (Russell, 1992). Indeed, a prior study found that lipid metabolism issues, like those related to cholesterol synthesis, might cause hepatotoxicity in the form of hepatic steatosis, liver enlargement, and weight gain. In fact, a prior study found that triclosan-treated animals with abnormalities in lipid metabolism, such as abnormalities in cholesterol synthesis, led to hepatotoxicity in the form of liver enlargement, weight gain, and steatosis through activating the peroxisome proliferator-activated receptors (PPAR). Furthermore, therapy with triclosan or diclosan in vivo had an impact on the levels of biomarkers linked to lipid metabolism, such as triglycerides. Triclosan and diclosan displayed comparable processes, while 1-chloro-3-(4-chlorophenoxy)benzene did not. This difference could be attributed to the fact that the hydroxyl group's presence or absence influences how these compounds interact with PPAR. However, a different classical hepatotoxicity [9].

Conclusion

The results of the current study suggest that drinking water contaminated with benzene, lead, and phenol may result in renal dysfunction as evidenced by increased serum levels of urea, creatinine, sodium, and potassium as well as decreased enzyme activity (ACP, ALP, and LDH) in tissues as seen in the test rat. As seen by the higher ALT, AST, GGT, and ALP activity as well as the decreased albumin and globulin levels, the polluted water may be compromising liver functioning [10].

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Potential conflicts of interest

The authors affirm that they have no known financial or interpersonal conflicts that would have appeared to have an impact on the research presented in this study.

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