Comparison of Halo- and Nitro-benzene Toxicity in Rat and Human Hepatocytes

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Abstract

The toxicity of halobenzenes is mediated by metabolites formed by oxidative metabolism. Quantitative structure-activity relationships (QSAR) were applied to evaluate the toxicity of halobenzenes congeners in rat and human hepatocytes. Toxicity was determined by incubating isolated cells with halobenzenes. Halobenzenes were effective at inducing toxicity in male rat hepatocytes, but not in human hepatocytes. In male hamster hepatocytes, halobenzenes also induced toxicity without an inhibition of microsomal cytochrome P450 activity as measured by the CO difference spectrum. In human hepatocytes, halobenzenes induced toxicity, but no inhibition of cytochrome P450 activity was observed. These results suggest that the toxicity of halobenzenes congeners in rat and human hepatocytes can be predicted using a QSAR approach. Human hepatocytes may be more resistant to halobenzenes toxicity than rat hepatocytes, which may be due to differences in cytochrome P450 expression and drug metabolism between rats and humans.

Materials and Methods

Halobenzene Toxicity: Halobenzenes were cytotoxic towards rat hepatocytes, but not human hepatocytes. Similar results were observed with 2,5- and 2,4-dibenzyl chloride. However, 1,2- and 1,4-dibenzyl chloride were cytotoxic towards both rat and human hepatocytes. In human hepatocytes, halobenzenes induced toxicity, but no inhibition of cytochrome P450 activity was observed. These results suggest that the toxicity of halobenzenes congeners in rat and human hepatocytes can be predicted using a QSAR approach. Human hepatocytes may be more resistant to halobenzenes toxicity than rat hepatocytes, which may be due to differences in cytochrome P450 expression and drug metabolism between rats and humans.

Results

QSAR analysis indicated that the cytotoxicity of halobenzenes congeners towards fresh rat hepatocytes and cryopreserved human hepatocytes correlated to low values of EHOMO. Compounds with low EHOMO energies more readily accept electrons, suggesting that nitroreductase catalyzed formation of an electrophilic reductive metabolite such as nitrosoarenes, is important in cytotoxicity. The resistance of human hepatocytes to nitrobenzenes may be attributed to lower nitroreductase activity and higher aromatic hydroxylation capacities. The results of this study suggest that the cytotoxicity of halobenzenes congeners towards fresh rat hepatocytes and cryopreserved human hepatocytes can be predicted using QSAR analysis. This suggests that the cytotoxicity of halobenzenes congeners towards fresh rat hepatocytes and cryopreserved human hepatocytes can be predicted using a QSAR approach. Human hepatocytes may be more resistant to halobenzenes toxicity than rat hepatocytes, which may be due to differences in cytochrome P450 expression and drug metabolism between rats and humans.

Conclusions

Human hepatocytes are more susceptible to halobenzene toxicity than rat hepatocytes. QSAR analysis indicated that the cytotoxicity of halobenzenes congeners towards fresh rat hepatocytes and cryopreserved human hepatocytes correlated to low values of EHOMO. This suggests that compounds with low EHOMO energies more readily accept electrons. The results of this study suggest that the cytotoxicity of halobenzenes congeners towards fresh rat hepatocytes and cryopreserved human hepatocytes can be predicted using QSAR analysis. This suggests that the cytotoxicity of halobenzenes congeners towards fresh rat hepatocytes and cryopreserved human hepatocytes can be predicted using a QSAR approach. Human hepatocytes may be more resistant to halobenzenes toxicity than rat hepatocytes, which may be due to differences in cytochrome P450 expression and drug metabolism between rats and humans.

References

ACNOWLEDGMENTS:

The International QSAR Foundation

Table 1. Log LD50 values of dinitrobenzene isomers towards cryopreserved rat and human hepatocytes.

<table>
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<th>Compound</th>
<th>Log LD50 [uM]</th>
<th>r2</th>
<th>S</th>
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<th>P</th>
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<td>+0.261</td>
<td>0.992</td>
<td>0.021</td>
<td>124.438</td>
<td>0.001</td>
</tr>
<tr>
<td>1,2-DNB</td>
<td>+0.400</td>
<td>0.992</td>
<td>0.021</td>
<td>124.438</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Figure 1. Representative structure of halobenzenes, X=Br or Cl. The structure was used as the basis for the QSAR study.

Figure 2. Dose response of dinitrobenzene toxicity in rat hepatocytes. The toxicity was determined by incubating isolated cells with halobenzenes. Halobenzenes were effective at inducing toxicity in male rat hepatocytes, but not in human hepatocytes. In male hamster hepatocytes, halobenzenes also induced toxicity without an inhibition of microsomal cytochrome P450 activity as measured by the CO difference spectrum.

Figure 3. Dose response of dinitrobenzene toxicity in human hepatocytes. The toxicity was determined by incubating isolated cells with halobenzenes. Halobenzenes were effective at inducing toxicity in male rat hepatocytes, but not in human hepatocytes. In male hamster hepatocytes, halobenzenes also induced toxicity without an inhibition of microsomal cytochrome P450 activity as measured by the CO difference spectrum.

Figure 4. QSAR derivation indicated that halobenzene induced toxicity in fresh rat hepatocytes. In addition, the cytotoxicity of halobenzene congeners towards cryopreserved rat and human hepatocytes was determined. In human hepatocytes, halobenzenes induced toxicity, but no inhibition of cytochrome P450 activity was observed. These results suggest that the toxicity of halobenzenes congeners in rat and human hepatocytes can be predicted using a QSAR approach. Human hepatocytes may be more resistant to halobenzenes toxicity than rat hepatocytes, which may be due to differences in cytochrome P450 expression and drug metabolism between rats and humans.

Figure 5. QSAR derivation indicated that halobenzene induced toxicity in fresh rat hepatocytes. In addition, the cytotoxicity of halobenzene congeners towards cryopreserved rat and human hepatocytes was determined. In human hepatocytes, halobenzenes induced toxicity, but no inhibition of cytochrome P450 activity was observed. These results suggest that the toxicity of halobenzenes congeners in rat and human hepatocytes can be predicted using a QSAR approach. Human hepatocytes may be more resistant to halobenzenes toxicity than rat hepatocytes, which may be due to differences in cytochrome P450 expression and drug metabolism between rats and humans.

Figure 6. QSAR derivation indicated that halobenzene induced toxicity in fresh rat hepatocytes. In addition, the cytotoxicity of halobenzene congeners towards cryopreserved rat and human hepatocytes was determined. In human hepatocytes, halobenzenes induced toxicity, but no inhibition of cytochrome P450 activity was observed. These results suggest that the toxicity of halobenzenes congeners in rat and human hepatocytes can be predicted using a QSAR approach. Human hepatocytes may be more resistant to halobenzenes toxicity than rat hepatocytes, which may be due to differences in cytochrome P450 expression and drug metabolism between rats and humans.

Figure 7. QSAR derivation indicated that halobenzene induced toxicity in fresh rat hepatocytes. In addition, the cytotoxicity of halobenzene congeners towards cryopreserved rat and human hepatocytes was determined. In human hepatocytes, halobenzenes induced toxicity, but no inhibition of cytochrome P450 activity was observed. These results suggest that the toxicity of halobenzenes congeners in rat and human hepatocytes can be predicted using a QSAR approach. Human hepatocytes may be more resistant to halobenzenes toxicity than rat hepatocytes, which may be due to differences in cytochrome P450 expression and drug metabolism between rats and humans.

Figure 8. QSAR derivation indicated that halobenzene induced toxicity in fresh rat hepatocytes. In addition, the cytotoxicity of halobenzene congeners towards cryopreserved rat and human hepatocytes was determined. In human hepatocytes, halobenzenes induced toxicity, but no inhibition of cytochrome P450 activity was observed. These results suggest that the toxicity of halobenzenes congeners in rat and human hepatocytes can be predicted using a QSAR approach. Human hepatocytes may be more resistant to halobenzenes toxicity than rat hepatocytes, which may be due to differences in cytochrome P450 expression and drug metabolism between rats and humans.