

Mechanistic View of Troglitazone Hepatotoxicity 311

- 1 Spiegelman, B. M. (1998). PPAR- γ : Adipogenic regulator and thiazolidinedione receptor. *Diabetes*
2 47: 507–514.
- 3 Tettey, J. N., Maggs, J. L., Rapeport, W. G., Pirmohamed, M. and Park, B. K. (2001). Enzyme
4 induction dependent bioactivation of troglitazone and troglitazone quinone *in vivo*. *Chem. Res.*
5 *Toxicol.* 14: 965–974.
- 6 Tirmenstein, M. A., Hu, C. X., Gales, T. L., Maleeff, B. E., Narayanan, P. K., Kurali, E., Hart,
7 T. K., Thomas, H. C. and Schwartz, L. W. (2002). Effects of troglitazone on HepG2 viability and
8 mitochondrial function. *Toxicol. Sci.* 69: 131–138.
- 9 Watanabe, T., Ohashi, Y., Yasuda, M., Takaoka, M., Furukawa, T., Yamoto, T., Sanbuissho, A. and
10 Manabe, S. (1999). Was it possible to predict liver dysfunction caused by troglitazone during the
11 nonclinical safety studies? *Iyakuhin Kenkyu* 30: 537–546.
- 12 Watanabe, Y., Nakajima, M. and Yokoi, T. (2002). Troglitazone glucuronidation in human liver and
13 intestine microsomes: high catalytic activity of UGT1A8 and UGT1A10. *Drug Metab. Dispos.* 30:
14 1462–1469.
- 15 Watanabe, I., Tomita, A., Shimizu, M., Sugawara, M., Yasumo, H., Koishi, R., Takahashi, T., Miyoshi,
16 K., Nakamura, K., Izumi, T., Matsushita, Y., Furukawa, H., Haruyama, H. and Koga, T. (2003). A
17 study to survey susceptible genetic factors responsible for troglitazone-associated hepatotoxicity
18 in Japanese patients with type 2 diabetes mellitus. *Clin. Pharmacol. Ther.* 73: 435–455.
- 19 Watkins, P. B. and Whitcomb, R. W. (1998). Hepatic dysfunction associated with troglitazone. *New*
20 *Engl. J. Med.* 338: 916–917.
- 21 Yamamoto, Y., Nakajima, M., Yamazaki, H. and Yokoi, T. (2001). Cytotoxicity and apoptosis pro-
22 duced by troglitazone in human hepatoma cells. *Life Sci.* 70: 471–482.
- 23 Yamamoto, Y., Yamazaki, H., Ikeda, T., Watanabe, T., Iwabuchi, H., Nakajima, M. and Yokoi, T.
24 (2002). Formation of a quinone epoxide metabolite of troglitazone with cytotoxic to HepG2 cells.
25 *Drug Metab. Dispos.* 30: 155–160.
- 26 Yamazaki, H., Shibata, A., Suzuki, M., Nakajima, M., Shimada N., Guengerich, F. P. and Yokoi, T.
27 (1999). Oxidation of troglitazone to a quinone-type metabolite catalyzed by cytochrome P-450
28 2C8 and P-450 3A4 in human liver microsomes. *Drug Metab. Dispos.* 27: 1260–1266.
- 29 Yoshigae, Y., Konno, K., Takasaki, W. and Ikeda, T. (2000). Characterization of UDP-
30 glucuronosyltransferases (UGTS) involved in the metabolism of troglitazone in rats and humans.
31 *J. Toxicol. Sci.* 25: 433–441.
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