Annex B

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Annex B: Immunotoxicity

In vitro

1. Sugiyama et al. (2013: abstract only) reported the effect of CIT on nitric oxide (NO) production by a mouse macrophage-like cell line RAW264 activated with lipopolysaccharide (LPS). One of the normal functions of NO is as a pro-inflammatory mediator and it plays a role in the protection from pathogens. LPS-induced NO release from RAW264 cells was inhibited by CIT and the transcription and expression of inducible NO synthase (iNOS) by LPS was suppressed by CIT. The author concludes that CIT may exert adverse effects in macrophages, indicating immunotoxic effects.

2. A study by Xu et al. (2022) investigated the effect of CIT (0, 60, 80, 240 and 270 µmol/L) on barrier and innate immune functions of the bovine mammary epithelium using a bovine mammary epithelial cell line (MAC-T). CIT exposure for 48 h significantly decreased cell viability in a concentration-dependent manner ($p < 0.05$) and IL-6 and TGF-β expression was downregulated ($p < 0.01$). Authors concluded that the results suggest CIT could potentially modulate barrier and innate immune functions of mammary epithelium.

3. In an in vitro experiment by Islam et al. (2012) CIT (1, 5, or 10 µg/ml for 6 hours) inhibited the IL-1β, IL-10, and TNF-α cytokine production in the RAW 264.7 murine macrophage cell line after pre-exposure to different toll-like receptor (TLR) ligands.

Repeat dosing

4. Islam et al. (2012) performed a study in which mice were administered CIT (1, 5, or 10 mg/kg bw) by gavage for 14 days. CIT treatment reduced the level of serum IgM but the production of IgA and IgE was increased in the highest CIT

treatment group compared to that of the control group, though this was not considered statistically significant. The IgG level did not change after CIT administration. Administration of CIT changed the regulation of the different immune cell populations in spleen, mesenteric lymph nodes (MLN) and small intestine. Results indicated that CIT induced apoptosis in the spleen, MLN and Peyer's patches (PP) by the change in the ratio of Bax/Bcl-2 activities. To assess the immunocompetence splenocytes and MLN cells from CIT treated mice were stimulated with ConA (T cell mitogen) or LPS (B cell mitogen). An increased proliferative capacity in ConA-induced splenocytes and MLN cells was noticeable in a dose-dependent manner indicating that CIT induced T-cell-specific lymphoproliferative capacity. Authors concluded that CIT has multiple immune modulatory effects in mice that may alter normal functions of immune system.

References:

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