

# ACC Review

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» *A distillation of best practice reflecting ACC's current position*

## Dioxin – Part 2

### Non-carcinogenic Health Effects

- » There is sufficient evidence to indicate that acute high level dioxin exposure can cause the skin condition chloracne
- » There is limited or suggestive evidence of a causal association with:
  - » Type II diabetes
  - » Peripheral neuropathy
  - » Porphyria cutanea tarda
  - » Spina bifida (in offspring)
- » Studies investigating a causal association with specific adverse health effects have a range of methodological limitations
- » It is currently not possible to accurately predict the lowest levels at which any given individual is likely to adversely respond to dioxin exposure.

## Background

This Review (Part 2) briefly describes the evidence supporting a causal association between exposure to 2,3,7,8-TCDD (with or without other dioxin-like compounds) and non-carcinogenic adverse health effects. It includes an overview of the characteristics of the evidence for non-carcinogenic and carcinogenic adverse health effects. The last Review in this series, Part 3, will summarise the evidence supporting a causal association between exposure and carcinogenic adverse health effects.

## Characteristics of the evidence

Data obtained from animal studies<sup>1,2</sup> suggests a dose-related increase between dioxin exposure and a wide spectrum of non-carcinogenic effects at the biochemical and cellular level. While this information is helpful, reliable extrapolation to humans is difficult due to inter-species differences. Human epidemiological evidence, therefore, is required for human risk-assessment.<sup>3</sup>

While a number of epidemiological studies have been carried out involving occupational or environmental dioxin exposures, the quality of the available evidence supporting a causal association with specific adverse health effects is variable. This is due to a number of methodological limitations, such as limited statistical power, difficulty in quantifying individual exposures, inadequate control of confounding factors, and insufficient latency periods and lengths of follow-up.

In general, the epidemiological studies that measure dioxin levels in the blood report levels in the lipid component of serum (lipid-adjusted serum levels) in picograms per gram of serum lipid (1 pg = 10<sup>-12</sup> g; so that pg/g = ng/kg = parts per trillion). Most studies estimate dioxin levels at the time of last exposure (e.g. a previous occupational or accidental source). Estimated levels are obtained by a process of back-extrapolation from current serum lipid levels, taking into account the half-life of the relevant dioxin(s) (usually TCDD) in the blood, and making allowance for the contribution of on-going background levels from food intake.

## Adverse non-carcinogenic effects

There is sufficient evidence to indicate that the skin condition chloracne is caused by high one-off TCDD exposure.<sup>2,13</sup> This effect may be related to up-regulation of receptor levels for epidermal growth factor (EGF). Other effects thought to be associated with acute high exposures include sleep disturbance, poor concentration, depression, and elevated serum cholesterol (and weight loss in test animals).<sup>12</sup>

There is limited or suggestive evidence that TCDD may increase the risk of (transient) peripheral neuropathy, porphyria cutanea tarda and, at high exposure levels, type II diabetes.<sup>2,13</sup> The relative risk (RR) of diabetes in a high exposure subgroup with current serum TCDD >33.3 pg/g was 2.5,<sup>4</sup> while a RR of 1.5 was found for those exposed to back-extrapolated levels above 94 pg/g.<sup>5</sup> A high prevalence of diabetes has been found in workers with current levels >1500 pg/g.<sup>6</sup>

There is inadequate and/or insufficient evidence to support an association with disorders/dysfunction of the following systems: cognitive or neuropsychiatric, motor or coordination (e.g. Parkinson's disease), chronic peripheral nervous, gastrointestinal, metabolic and digestive (e.g. lipid abnormalities<sup>7</sup>), circulatory, respiratory (AL amyloidosis), and immune (e.g. autoimmunity), or with endometriosis and thyroid homeostasis.<sup>2,13</sup>

Findings regarding reproductive effects are conflicting.<sup>8</sup> One of the better studies of paternal exposures<sup>9</sup> found no significant increased risk for spontaneous abortion, stillbirths, major birth defects, or developmental delays, and no dose-response relationship. However, while this study utilised well documented information and serum dioxin measurements collated over a 25 year post-exposure period, it lacked the power to detect elevations in specific male-mediated birth defects. There is inconsistent evidence of a dose-related decrease in testosterone and increase in gonadotrophins.<sup>10</sup> There is some data to suggest a dose-related alteration in the sex ratio of newborns of fathers younger than 19 years at the time of exposure.<sup>11</sup>

In pregnancy, the embryo/foetus is affected at doses lower than those maternally toxic. There is limited or suggestive human evidence of an association with spina bifida, and inadequate or insufficient data regarding all other birth defects.<sup>2</sup> Infants exposed through breast milk may exhibit alterations in thyroid hormone levels and possibly neurobehavioural and neurological deficits.

## Levels of exposure and health effects<sup>9</sup>

It is currently not possible to accurately predict the lowest levels at which any given individual is likely to adversely respond. This is due to the lack of detailed and, at times, conflicting information on the relative risks of various adverse effects as a function of exposure. It is likely that the probability of non-carcinogenic effects increases proportionally to increases in body burden and dose to target tissues. This suggests a linear relationship between exposure and effect.

## References

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