Hydrogen Cyanamide – Prenatal Developmental Toxicity Study by the Oral Route (gavage) in the Rat

Oral (gavage) administration of Hydrogen Cyanamide to Sprague-Dawley rats from days 6 to 19 of gestation at doses of 3, 15 and 45 mg/kg bw/day led to a severe maternal toxicity in the **high dose group** with a rapid onset and sustained reduced mean body weight gain, leading to body weight loss during the first 6 days (GD 6 to GD 12). Reduced food consumption in the high dose group resulted in a 27 % lower mean terminal body weight compared with the control (net body weight loss [i.e. maternal body weight change from GD 6 to GD 20 minus gravid uterus weight] of 34 g in the 45 mg/kg bw/day group compared with net body weight gain of 48 g in the control) and pronounced clinical signs (piloerection, decreased activity, intermittent whole body tremors and pale faeces). Although there was no mortality, a premature sacrifice was considered for three females in the high dose group (45 mg/kg bw/day) due to the severe maternal toxicity.

Foetal development was clearly compromised in the high dose group (45 mg/kg bw/day) with a marked reduction in foetal weight, a delayed testicular descent, a delay in ossification of axial and appendicular skeletal bones and rib anomalies.

Consistent with the degree of maternal toxicity, as described by Danielsson BR (2013), there was clear evidence of developmental toxicity and delay in the development in the 45 mg/kg bw/day group with markedly reduced mean foetal weight (-38 %), widespread incomplete/absent ossification of axial and appendicular skeletal bones and thickened and/or wavy ribs (7 % and 31 %, respectively) compared with the control. Also consistent with the low foetal weight and the delay in the development there were 7 foetuses from 7 litters with a malpositioned (not completely descended) testis.
However, within the context of this study, it is not possible to establish if other developmental effects (small diaphragmatic hernia with no impact on the lung size and great blood vessel changes) can be attributed to the marked maternal toxicity and the compromised foetal well-being.
However, due to the severe maternal toxicity observed at 45 mg/kg bw/d, the regulatory value of the data in this group is of limited value for determining developmental effects.

Moderate maternal toxicity was observed in the **mid dose group** (15 mg/kg bw/d**)** with a 9 % average reduction in mean food consumption during the dosing period and a 6 % lower terminal mean body weight compared with the control. The only developmental effect clearly attributable to treatment in this group was a slight reduction in mean foetal weight in comparison with the concurrent control (-8 %) (resulting in lower mean gravid uterus weight of 13 % compared with the control).

The **low dose** of 3 mg/kg bw/day is a no observed effect level (NOEL) for both maternal and embryo-fetal toxicity.