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Effect of maternal feed restriction on prenatal development in rats and rabbits – A review of published data

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ABSTRACT

With respect to hazard classification for developmental toxicity under the CLP Regulation it is important to consider the possible influence of maternal toxicity. The aim of the present review was to characterize to which extent developmental effects could be caused by non-specific maternal toxicity. Such effects would not be relevant for classification. In prenatal developmental toxicity studies, the administration of high doses is given in the guideline. The associated non-specific systemic toxicity often affects the maternal body weight. Therefore, published results of studies in rats and rabbits, where maternal weight gain during gestation was inhibited by restricted feeding, were examined regarding developmental effects. In summary, maternal feed restriction resulted in a reduction of fetal body weight that was sometimes accompanied by delayed ossification in both species. Considering their magnitude these effects could be interpreted as secondary non-specific (i.e. not caused by a developmental toxicant) effects. Based on the limited number of available publications in total no further consequences on prenatal development by maternal feed restriction were observed.

1. Introduction

Before placing chemicals on the European market an assessment of the potential risks to human health and the environment is mandatory (EC, 2016). In line with the identified hazards, substances have to be classified and labeled according to the Regulation (EC) No. 1272/2008 on classification, labelling and packaging of substances and mixtures (CLP Regulation) (EC, 2015). Reproductive toxicity is one of the hazard classes and further differentiated into i) adverse effects on sexual function and fertility and ii) adverse effects on development. Tests for generating information on intrinsic properties of substances are conducted in accordance with international accepted test methods like OECD test guidelines (TG). The OECD TG 414 "*Prenatal Developmental Toxicity Study*" is designed to provide information concerning the effects of prenatal exposure of pregnant animals on the developing organism (OECD, 2001). It requires including the administration of doses that are high enough to clearly induce signs of maternal toxicity. The term "maternal toxicity" encompasses a range of adverse effects in the pregnant animal like clinical signs of overt toxicity (e.g. ataxia) or a decrease in body weight. The idea is not to miss any adverse effect on prenatal development due to the selection of low doses only. However, the interpretation of the developmental outcome is often difficult at doses causing maternal toxicity. The development of the conceptus in utero can be influenced by toxic effects in the mother either through mechanisms related to stress, or by other specific maternally-mediated mechanisms. For the conclusion on classification for developmental toxicity the influence of maternal toxicity has to be evaluated. Where it can be clearly demonstrated that any fetal effects are secondary non-specific (i.e. not caused by a developmental toxicant) effects, depending on the severity of the effects, classifying the chemical as a developmental toxicant is not warranted (EC, 2015).

For decades a debate is going on among toxicologists concerning the influence of maternal toxicity on the development of the offspring (Beyer et al., 2011; Chahoud et al., 1999b; Chernoff et al., 1989; Chernoff et al., 2008; Danielsson, 2013; ECETOC, 2004; Kimmel et al., 1987; Paumgartten, 2010). This discussion has been stimulated by a publication of Khera in the eighties. Khera analyzed data from 234 teratology studies of chemical and physical agents in hamsters, mice, rats, and rabbits. Based thereon, it was postulated that a number of effects seen in the conceptus (e.g. embryo-fetal death, certain malformations) only occurred as a consequence of maternal toxicity (Khera, 1985). In contrast, Chahoud et al. analyzed data from teratology studies in rats and concluded that maternal

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toxicity does not always led to developmental toxicity (Chahoud et al., 1999b). Chernoff et al. reviewed data of 125 developmental toxicity assays in mice, rats, and rabbits and found a relationship between reduced maternal body weight gain and lower fetal body weight (Chernoff et al., 2008). Based on the literature, a consistent relationship between developmental effects and general maternal toxicity reflected as reduced maternal body weight or body weight gain could not be demonstrated. It was recommended by Chahoud et al. that findings should be evaluated on a case-by-case basis (Chahoud et al., 1999b) which makes consistency across cases exceptionally difficult. Furthermore, criteria for an appropriate interpretation of developmental effects occurring in the presence of maternal toxicity have to be defined, which was discussed at the ECETOC workshop on "*Influence of Maternal toxicity in Studies of Developmental Toxicity*" held 2004 in Berlin (ECETOC, 2004).

The aim of this work is to provide support in the interpretation of findings in developmental toxicity studies. As mentioned above, regulatory guidance requires the demonstration of maternal toxicity in at least one dose group, which is commonly exhibited by altered maternal body weight gain during pregnancy. The presented evaluation was conducted to generate information to aid in differentiating fetal effects which are secondary to altered maternal body weight during gestation from those which may be caused by a specific mechanism of the compound under study. For this purpose, published data on developmental toxicity studies in rats and rabbits where maternal body weight gain during gestation was impaired by restricted feeding were analyzed. Developmental data from chemical-treated animals were not considered in this review.

2. Methods

A literature search in Pubmed (http://www.ncbi.nlm.nih.gov/pubmed/) using the terms "food restriction", "food deprivation", "dietary restriction", "developmental toxicity" and "terato*" in variable combinations was carried out in July 2015. The resulting studies retrieved for this work were conducted between 1965 and 2009. 17 studies were performed with rats and six with rabbits. However, due to insufficient description of the results only 12 out of the 17 studies with rats were included for evaluation. In addition to studies with feed restriction, studies on substance-specific developmental toxicity which included a control group with limited feed intake were considered in this review due to the scarcity of published studies focusing solely on the developmental effects of feed restriction. Only the data of the control group and feed-restricted control group of these studies were included in this data analysis. The relevant individual data are provided summarized in tabular form (see Supplementary material). For data analysis quantitative data partially had to be calculated from the original data or needed to be extracted from graphs. For this reason, an indication of statistical significance was not always possible. These data are given in italics in the tables of supplementary material. No additional statistical analyses were performed.

As an indicator for maternal toxicity the maternal body weight was used. According to the CLP Regulation four different parameters can be considered – maternal body weight, corrected maternal body weight at the end of gestation, maternal body weight gain or corrected maternal body weight gain during gestation. Corrected maternal body weight/body weight gain is the maternal body weight/body weight gain minus the gravid uterine weight (EC, 2015). It has to be noted that the corrected maternal body weight/body weight gain may indicate whether the effect is maternal or intrauterine. Therefore, for this paper the corrected maternal body weight/body weight gain as an indicator for maternal toxicity was selected. In the publications data on gravid uterine weight were often absent. In this case the gravid uterine weight was estimated using the litter size, fetal body weight and placental weight. In the absence of information on placental weight calculation was based on the assumption of 1 g for rats and 5 g for rabbits.[1]

To determine the impact of limited maternal feed intake and the resulting maternal body weight/body weight gain all documented effects on prenatal development (fetal body weight, resorption, fetal death, reduced ossification, malformation) were analyzed. Because historical control data from the specific laboratory were missing in the evaluated studies, the evaluation of effects on prenatal development was based on historical control data from literature.

3. Results

3.1. Feed restriction in pregnant rats

Table 1 summarizes the results of 12 publications dealing with the impact of maternal feed restriction on prenatal development in rats. Predominantly Sprague-Dawley (SD) rats were used in these studies (Ahokas et al., 1981, 1983; Anderson et al., 1980; Beall and Klein, 1977; Berg, 1965; Chahoud et al., 2002; Fleeman et al., 2005; Hastings-Roberts and Zeman, 1977; Kawaguchi et al., 1994; Lederman and Rosso, 1980, 1981a, 1981b). A maximum of 75% less feed was given compared to the control group. Most studies examined a reduction in amount of provided feed by 50% compared to that of the control group. Only two investigated a dose-response-relationship (Berg, 1965; Fleeman et al., 2005). In three studies the feed restriction was maintained throughout the period of organogenesis and afterwards rats were allowed *ad lib.* access to feed (Beall and Klein, 1977; Fleeman et al., 2005; Kawaguchi et al., 1994). The feed restriction in all other studies was maintained until the end of gestation. In Table 1 data on corrected maternal body weight/body weight gain are presented as percentage of the control group. All studies showed that a limited maternal feed intake resulted in a reduced corrected maternal body weight at the end of gestation. This effect was less pronounced when feed restriction occurred only during organogenesis (Fig. 1). Moreover, data for corrected maternal body weight gain until the end of gestation showed that a feed restriction of at least 50% of the control group resulted not only in a reduced corrected maternal body weight gain but even in a body weight loss. Therefore, the quantification of corrected maternal body weight gain as parameter of maternal toxicity was considered inadequate. Instead, the corrected maternal body weight at the end of gestation was used for further evaluation.

A feed restriction down to 50% during gestation resulted in a reduction of corrected maternal body weight at the end of gestation of 24–36% compared to the control group. A decrease in fetal body weight of 12–25% was observed in the offspring of these animals (Ahokas et al., 1981, 1983; Anderson et al., 1980; Berg, 1965; Chahoud et al., 2002; Lederman and Rosso, 1980, 1981a, 1981b). Thus, malnourishment of the dams resulted in a decrease of fetal growth. Abortion, the expulsion of a fetus before it is viable, was not observed in any restricted feeding study with rats.

The relative reduction of the corrected maternal body weights was higher than the relative reduction of fetal body weights. This indicates that, in rats, a maternal body weight reduction does not affect the fetal growth at the same magnitude. That means, the

[1] Personal communication to Ana-Maria Klaus, Bayer Pharma AG, Wuppertal, Germany: The placental weight for Wistar rat is around 0.6–0.7 g. For the sake of simplicity the mean placental weight was rounded to 1 g for the calculations in this review. Placental weight for rabbit was estimated based on available quantitative data from the publications.