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Commentary

Reproductive and developmental toxicity testing: Examination of the extended one-generation reproductive toxicity study guideline

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ABSTRACT

An important aspect of safety assessment of chemicals (industrial and agricultural chemicals and pharmaceuticals) is determining their potential reproductive and developmental toxicity. A number of guidelines have outlined a series of separate reproductive and developmental toxicity studies from fertilization through adulthood and in some cases to second generation. The Extended One-Generation Reproductive Toxicity Study (EOGRTS) is the most recent and comprehensive guideline in this series. EOGRTS design makes toxicity testing progressive, comprehensive, and efficient by assessing key endpoints across multiple life-stages at relevant doses using a minimum number of animals, combining studies/evaluations and proposing tiered-testing approaches based on outcomes. EOGRTS determines toxicity during preconception, development of embryo/fetus and newborn, adolescence, and adults, with specific emphasis on the nervous, immunological, and endocrine systems, EOGRTS also assesses maternal and paternal toxicity. However, EOGRTS guideline is complex, criteria for selecting doses is unclear, and monitoring systemic dose during the course of the study for better interpretation and human relevance is not clear. This paper discusses potential simplification of EOGRTS, suggests procedures for relevant dose selection and monitors systemic dose at multiple life-stages for better interpretation of data and human relevance.

1. Background

In order to provide a background for discussion of the EOGRTS guidance, the readers should be aware of several other guideline studies routinely conducted, primarily in rats, to determine immediate and latent reproductive effects of chemical exposure. Assessment of toxicity to reproduction includes possible effects of chemicals on fertility, embryonic and fetal development, peri- and postnatal development, and maternal function. Traditionally, separate reproductive/developmental toxicity studies are conducted to evaluate these effects. Guidelines OECD 414 and OPPTS 870.3700 determine effects of chemicals on embryo-fetal development/death, altered growth and structural changes (ICH, 2005; OECD, 2001a; USEPA, 1998a). Effects of chemicals on maternal behavior, length of gestation, dystocia, number and sex of pups, live births, runts, presence of gross abnormalities, and abnormal behavior in pups are determined in guidelines OECD 421 (screening test) and OPPTS 870.3550 (ICH, 2005; OECD, 1995; USEPA, 2000a). General and reproductive/developmental toxicity endpoints are combined in OECD 422 (screening test) and OPPTS 870.3650 guidelines (OECD, 1996; USEPA, 2000b).

Guidelines OECD 415 and 416 determine effects of chemicals on reproduction in one- and two-generation studies, respectively (OECD, 1983, 2001b; USEPA, 1998b). The two-generation study (OECD 416; OPPTS 870.3800) is considered the most comprehensive design to assess reproductive toxicity (Carney and Sattivari, 2013) and the effects of chemicals on the reproductive performance of the F1 parents. The two-generation study assesses effects of chemicals on reproductive parameters listed for OECD 421 in P and F1 generations as well as the presence of gross abnormalities and abnormal behavior in F1 and F2 animals. The NTP's modified one-generation study design determines effects of chemicals on animals from gestation through weaning of F2 animals (Foster, 2014); however, no formal guideline document exists. The difference between the NTP design and other approved guidelines include retention of multiple pups per litter rather than 1 pup/sex/litter/dose group and premating treatment of males for a full 10

Abbreviations: EOGRTS, Extended One-Generation Reproductive Toxicity Study; DNT, Developmental Neurotoxicity; DIT, Developmental Immunotoxicity.

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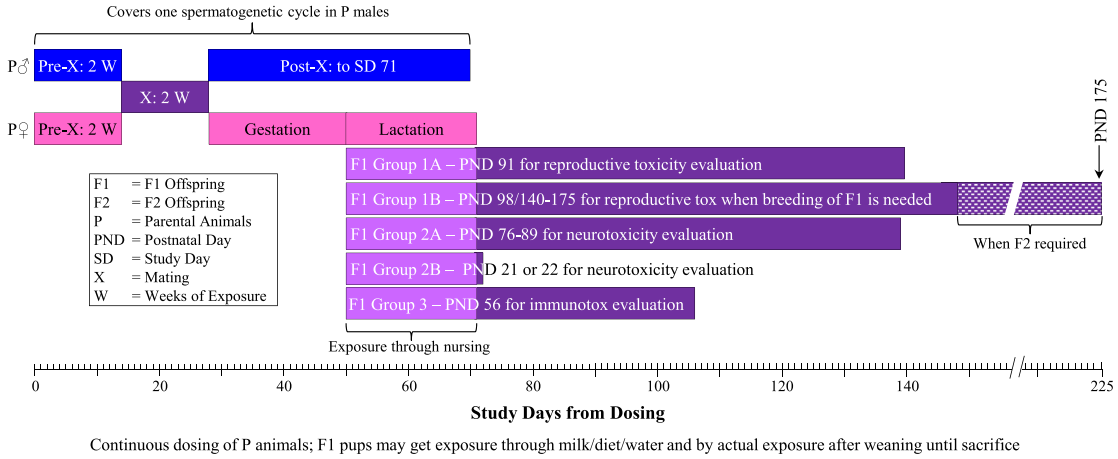

Fig. 1. Graphic depiction of the current EOGRTS (OECD 443) design.

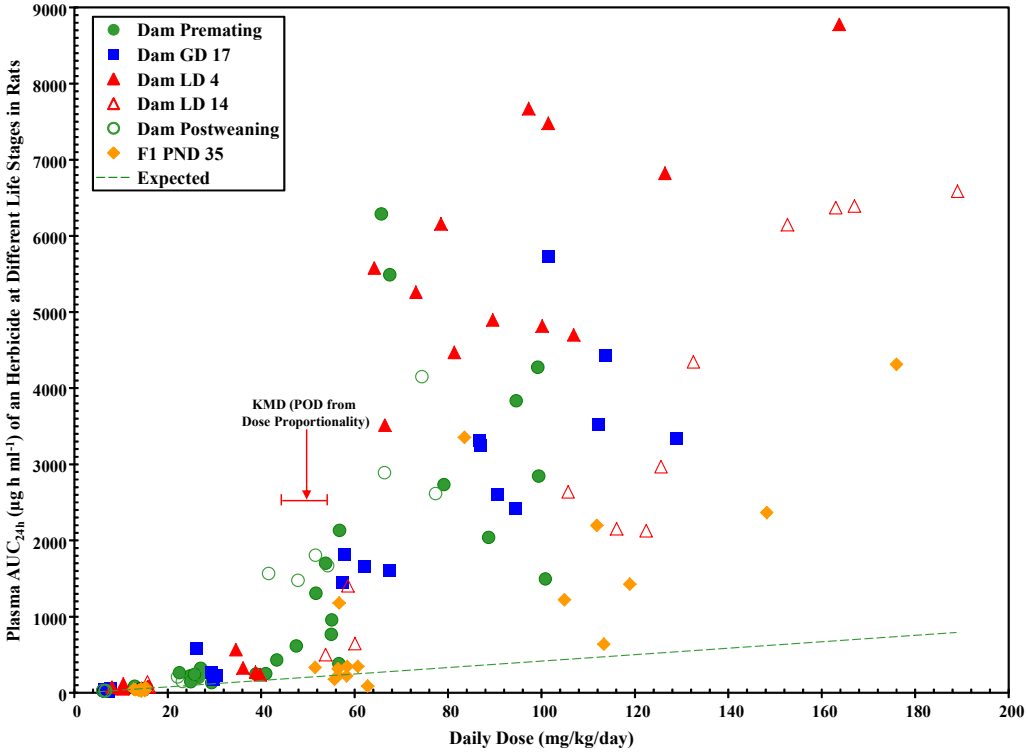

Fig. 2. Change in systemic dose of a herbicide (2,4-D) in rats at different life stages and determination of the kinetically-derived maximum dose (modified from Saghir et al., 2013).

weeks. However, both ICH and OECD guidelines indicate that a full 10-week premating period is often not needed, especially when other general toxicity studies (e.g., existing subchronic studies) indicate a lack of toxicity to the testes or uterus.

2. Current guidelines and modified approach

Most of the above described individual guidelines evaluate toxicity of chemicals to only parts of the reproductive and developmental stages with the exception the two-generation reproductive toxicity study. These guideline studies have not been updated to reflect advancements in the assessment of developmental and reproductive toxicity. For example, researchers now like to combine multiple reproductive and developmental toxicity studies into a single study and determine systemic exposure during dose range-finding or other general toxicity studies for the selection of appropriate doses (Chapman et al., 2013; Dorato et al., 2014; Marty et al., 2013; Saghir et al., 2013). Although the two-generation toxicity study is considered “the gold standard” for the assessment of reproductive toxicity, it is complex in design, high in the utilization in animals (~2600 animals for study in rats) and with debatable value of the F2 generation (Janer et al., 2007a, 2007b; Moore et al., 2009; Piersma et al., 2011; Rorije et al., 2011). The two-generation toxicity study is also not designed to evaluate developmental neurotoxicity (DNT) or developmental immunotoxicity (DIT) endpoints, which require standalone studies using an additional 1280 animals.