Methylphenidate and Its Salts

Methylphenidate and its salts, such as methylphenidate hydrochloride (Ritalin), are commonly prescribed psycho-stimulants used in the treatment of attention deficit/hyperactivity disorder in children and adults. Methylphenidate is also used to treat narcolepsy.

Methylphenidate and its salts passed the animal data screen, underwent a preliminary toxicological evaluation, and are being brought to the Carcinogen Identification Committee for consultation. This is a compilation of the relevant studies identified during the preliminary toxicological evaluation.

Epidemiological data

- Cohort studies
  - Members of Kaiser Permanente health plan in the San Francisco Bay Area and Central California, 1991 – 2003 (35,400 methylphenidate users under the age of 20 years): Oestreicher *et al*. (2007)
    - *Elevated standardized morbidity ratio for lymphocytic leukemia in child methylphenidate users*
  - Members of Kaiser Permanente health plan in the San Francisco Bay Area, 1969 – 1973 (529 methylphenidate users of any age): Selby *et al*. (1989)
    - *No increase in cancer risk in subjects receiving methylphenidate*

Animal carcinogenicity data

- Two-year dietary studies
  - Male and female B6C3F_1 mice: NTP (1995)
    - *Liver tumors (by pairwise comparison and trend) in males and females*
  - Male and female F344/N rats: NTP (1995)
    - *No treatment-related tumor findings*

- Transgenic mouse studies
  - 24-week dietary studies in male and female transgenic p53(+/-) mice: Freeman *et al*. (1998)
    - *No treatment-related tumor findings*
  - 24-week dietary studies in male and female Tg.AC transgenic mice: Freeman *et al*. (1998)
    - *No treatment-related tumor findings*

Other relevant data

- Genotoxicity
    - SCE, CA, and MN in lymphocytes of exposed children (*positive and negative*): El-Zein *et al*. (2005); Witt *et al*. (2008); Ponsa *et al*. (2009); Walitza *et al*. (2010)
    - DNA damage in rat cells *in vivo (positive and negative*): Andreazza *et al*. (2007); Witt *et al*. (2010)
    - Sister chromatid exchanges (SCE) and chromosome aberrations (CA) in Chinese hamster ovary cells *(positive)*: NTP (1995, p. 5, 56); NTP (2005, pp. II-34 – II-35)
    - Mutagenicity in *S. typhimurium (negative)*: NTP (1995, p.7, 56); NTP (2005, pp. II-34 – II-35)
    - Mutagenicity in *E. coli (negative*): NTP (2005, pp. II-34 – II-35)
    - Mutagenicity in mouse lymphoma cells *(negative)*: NTP (2005, pp. II-34 – II-35)
    - Induction of unscheduled DNA synthesis in rat hepatocytes *in vitro (negative)*: Mirsalis *et al*. (1983)
    - Transformation assay in BALB/c-3T3 cells *(negative)*: NTP (2005, pp. II-35)
    - Mutations in Big Blue mice *in vivo (negative*): Manjanatha *et al.* (2009)
    - HIS49 Pig-A mutations in red blood cells of rats exposed *in vivo (negative)*: Dobrovolsky *et al*. (2010)
    - Micronuclei (MN) in mouse bone marrow and peripheral blood erythrocytes *in vivo (negative)*: NTP (2005, p. II-35); Manjanatha *et al*. (2009)
    - MN in rat blood cells *in vivo (negative*): Andreazza *et al*. (2007); Dobrovolsky *et al*. (2010); Witt *et al*. (2010)
    - HPRT mutation, MN, and CA in male rhesus monkeys *in vivo (negative)*: Morris *et al*. (2009)

- Mechanistic considerations
    - CA as a biomarker of cancer risk: Bonassi *et al*. (2008)

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