



NTP
National Toxicology Program

NTP Study Nomination: Hydroxyurea

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NTP Board of Scientific Counselors Meeting

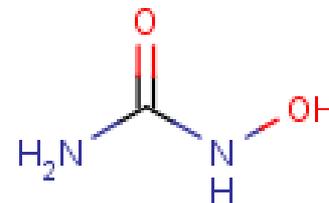
November 20-21, 2008





Hydroxyurea

- Inhibits ribonucleotide reductase, leading to inhibition of DNA synthesis and S-phase cytotoxicity, and ultimately increased production of hemoglobin F



- Clinical use
 - Branded and generic hydroxyurea products
 - Approved to treat sickle cell disease (1998) and certain cancers (1967) in adults
 - Off-label use to treat myeloproliferative disorders, thalassemia, HIV infection
 - Off-label use and active clinical investigation as sickle cell therapy in children
 - Not recommended for use during pregnancy
 - Long-term therapy



Hydroxyurea Nomination

- Nominated by a Private Individual and the NIEHS based on:
 - Wide use in the treatment of sickle cell anemia and myeloproliferative diseases
 - Demonstrated mutagenicity and clastogenicity
 - Lack of robust carcinogenicity studies and concern regarding safety associated with long-term use
 - Critical data need identified by the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR) Expert Panel
 - Multi-generation experimental animal studies to assess the long-term effects of prenatal and postnatal exposures on postnatal development including developmental neurotoxicity, reproductive function, and carcinogenicity



Hydroxyurea: Toxicological Data

- Carcinogenic potential
 - Unequivocal genotoxicant
 - Case reports of acute leukemia and skin cancers; increased incidence of acute leukemia and myelodysplastic syndrome in small cohort studies
 - Increased incidence of mammary tumors in female rats (i.p. injection)
 - Inadequate evidence for carcinogenicity in humans or experimental animals
 - IARC (2000): Group 3 “not classifiable as to its carcinogenicity to humans”
- Reproductive and developmental toxicity (NTP CERHR, 2008)
 - Few case reports of low sperm count, decreased sperm motility
 - Adverse effects on development and male reproductive tract in experimental animal studies
 - Malformations, reduced numbers of live births, fetal growth abnormalities
 - Decreased testis weight and histologic abnormalities of seminiferous tubules in rats and mice; decreased sperm counts in mice
 - Blood concentrations associated with some of these effects in animals similar to those in patients on therapy



Hydroxyurea: Key Issues

- Potential developmental, reproductive, and carcinogenic hazard associated with hydroxyurea treatment recognized (strong label warning)
- Long term experimental studies to fully understand effects on fertility, developmental outcomes and carcinogenicity lacking, particularly for chronic exposure beginning early in life
- Data inadequacies acknowledged but is only approved, efficacious therapy for a serious disease (risk benefit consideration)
- Value of additional animal studies in modifying clinical treatment guidelines
- NIH Consensus Development Conference
 - Risks considered acceptable compared to the risks of untreated sickle cell disease
 - Identified need for further studies (experimental animal studies not specified) to provide more information about adverse developmental and reproductive effects and carcinogenic risk



Hydroxyurea Study Recommendations

- Initial recommendation for no additional experimental animal toxicity studies at this time
- Currently ongoing and planned clinical trials, and additional prospective human studies that may be initiated in the future may address outstanding safety concerns associated with chronic hydroxyurea treatment
 - Research needs identified in CERHR, AHRQ, NIH Consensus Development Conference reports
- NTP will monitor research progress in this area and if necessary, revisit the need for rodent toxicology studies



Questions and Comments

NTP CERHR Conclusions (Draft Brief, March 2008)

- Reproductive toxicity in men
 - *Serious concern for adverse effects*
- Developmental toxicity (fetus)
 - *Concern for adverse effects*
- Developmental toxicity (growth and development in children 5-15 years of age)
 - *Minimal concern for adverse effects*
- Developmental toxicity (infants and children under 5 years of age)
 - *Insufficient hazard and/or exposure data*
- Reproductive toxicity in women
 - *Insufficient hazard and/or exposure data*