

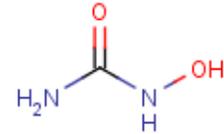
# NTP Research Concept: Hydroxyurea

## Project Leader:

Barry McIntyre, NTP/Toxicology Branch

## Nomination Background and Rationale:

Hydroxyurea was nominated to the NTP for toxicological testing by a private citizen and the NIEHS (based on the findings from the CERHR report- see below). The NTP Interagency Committee for Chemical Evaluation and Coordination (ICCEC) recommended deferral of the hydroxyurea nomination in January 2008. The initial nomination was reviewed by the Board of Scientific Counselors (BSC) in November 2008, and the NTP recommended (and the BSC concurred) that no additional work should be done at that time. Subsequently, a NIH Consensus Development Conference on Sickle Cell Disease indicated that additional studies in animals would be beneficial to characterize adverse developmental and reproductive effects and carcinogenic risks of hydroxyurea. In addition, clinical trials in infants and children are being funded by NIH. FDA supports the conduct of additional animal studies.



Hydroxyurea, also called hydroxycarbamide, is marketed as Hydrea® and Droxia® by Bristol-Myers Squibb; several FDA-approved unbranded (generic) hydroxyurea products are also available. Hydroxyurea has been used to treat melanoma, chronic myelocytic leukemia, ovarian cancer, squamous cell carcinoma, as well as being used chronically to treat sickle cell anemia. Hydroxyurea is an approved treatment for adults with sickle cell disease; however, hydroxyurea is being prescribed off-label with an increasing frequency in young children and infants (including pregnant women), to treat sickle cell anemia. Clinical trials are currently ongoing to characterize the clinical safety and efficacy in this population of patients. Moreover, there are no other approved drug therapies available, and given the anticipated therapeutic benefit that will be demonstrated in these ongoing clinical trials, it is likely that this therapeutic intervention will become more common.

Hydroxyurea inhibits the enzyme ribonucleotide reductase, which catalyzes the conversion of ribonucleotides to deoxyribonucleotides. The depletion of deoxyribonucleotide pools is not complete but is sufficient to inhibit deoxyribonucleic acid (DNA) synthesis, resulting in S-phase cytotoxicity<sup>(1)</sup>. The use of hydroxyurea in the treatment of sickle cell disease was initially based on the observation that cytotoxic agents increase the production of fetal (F) hemoglobin. The mechanism by which hydroxyurea increases hemoglobin F production is incompletely understood. It has been proposed that hydroxyurea produces a transient arrest in erythropoiesis followed by a recovery period, during which more immature progenitors that have not yet lost their ability to synthesize hemoglobin F are recruited. Hemoglobin F inhibits the polymerization of hemoglobin S, resulting in milder clinical manifestations of sickle cell disease<sup>(2-5)</sup>.

Studies in laboratory animals have demonstrated that hydroxyurea affects rapidly dividing cells (bone marrow, lymphoid tissue, GI, germinal epithelium) including those in the embryo/fetus and is a multispecies teratogen (warning on the FDA label). There is also some evidence that hydroxyurea affects rodent fertility and immune and neural cell populations, as well as impacting neurobehavioral development in rodents. Moreover, the plasma level of hydroxyurea in humans as compared to the plasma level where toxicity is observed in animals is near unity<sup>(6)</sup>. Nevertheless, the potential for hydroxyurea to affect the developing human organ systems is unknown.

Hydroxyurea is considered an unequivocal genotoxicant and has a “black box” warning indicating a potential for carcinogenic risk<sup>(7)</sup>. However, there is inadequate evidence for carcinogenicity in humans or experimental animals, and the IARC considers hydroxyurea “not classifiable as to its carcinogenicity to humans (Group 3). Nevertheless, individuals who are treated with this therapy are at a higher risk of developing secondary cancers. Since clinical use of hydroxyurea may begin early (*in utero*/infant) and continue over a lifetime, additional animal data will aid in determining the potential risk of hydroxyurea “lifetime” exposure.

The CERHR expert panel that reviewed the hydroxyurea literature recommended that:

Experimental animal studies are needed to evaluate long term effects of prenatal and postnatal hydroxyurea exposures (separately and together) on postnatal development, including (but not limited to) developmental neurotoxicity, reproductive function, and carcinogenesis. Studies with a multi-generation design with an oral route of exposure would help meet this need.<sup>(8)</sup>

Moreover, in a statement by an independent scientific panel following a NIH Consensus Development Conference on Sickle Cell Disease, further studies were recommended to provide more information about adverse developmental and reproductive effects and carcinogenic risk<sup>(9)</sup>.

### **Key Issues:**

Hydroxyurea is being used with increasing frequency in young children and infants for the treatment of sickle cell anemia and related diseases. Hydroxyurea is also used in the treatment of some forms of cancers. There is limited information on the potential long-term consequences of hydroxyurea use in infants, children and adults. Data generated in rodents would provide vital information to clinicians in counseling patients on the risks and benefits of this therapy.

### **Proposed Approach:**

We hypothesize that toxic effects will be observed following exposure to hydroxyurea and that the prenatal and neonatal developmental periods will be particularly sensitive to the adverse effects of this drug. We further hypothesize that the immune, nervous, and reproductive systems will show developmental abnormalities and long-term adverse effects. The goal of this research program is to test these hypotheses by generating toxicity information in rodents exposed to hydroxyurea beginning in gestation. The offspring would be assessed for the following endpoints:

- Malformations, litter size, etc.
- Neural-behavioral assessment
- Fertility (including reversibility/recovery)
- Immune function
- Carcinogenicity
- Exposure

#### *Tier 1*

Dose pregnant rats late in gestation (dosing earlier will result in extensive terata/resorptions) and dose the subsequent offspring directly. The endpoints above (with exception of carcinogenicity) would be assessed in the F1 and F2 generations.

#### *Tier 2*

Conduct perinatal carcinogenesis study in the rat, standard 2 year bioassay in the mouse. Results from Tier 1 would be used to assist in the dose selection for Tier 2.

#### **Significance and Expected Outcome:**

The expected data will provide critical information on long-term outcomes to aid in risk-benefit decisions. These data to advise the health authorities and the medical community regarding hazard and risk. In addition, a better understanding of the mode of action and risk/benefit may help spur research in developing a better therapy for sickle cell disease.

#### **References:**

1. Koç, A., Wheeler, L. J., Mathews, C. K. and Merrill, G. F. Hydroxyurea arrests DNA replication by a mechanism that preserves basal dNTP pools. *J Biol Chem* 2004; 279: 223-30.
2. Charache, S., Barton, F. B., Moore, R. D., Terrin, M. L., Steinberg, M. H., Dover, G. J., Ballas, S. K., McMahon, R. P., Castro, O. and Orringer, E. P. Hydroxyurea and sickle cell anemia. Clinical utility of a myelosuppressive "switching" agent. The Multicenter Study of Hydroxyurea in Sickle Cell Anemia. *Medicine* 1996; 75: 300-26.
3. Bunn, H. F. Pathogenesis and treatment of sickle cell disease. *N Engl J Med* 1997; 337: 762-9.
4. Yang, Y. M. and Pace, B. Pharmacologic induction of fetal hemoglobin synthesis: cellular and molecular mechanisms. *Pediatr Pathol Mol Med* 2001; 20: 87-106.
5. Fixler, J. and Styles, L. Sickle cell disease. *Pediatr Clin North Am* 2002; 49: 1193-210
6. Liebelt EL, Balk SJ, Faber W, Fisher JW, Hughes CL, Lanzkron SM, Lewis KM, Marchetti F, Mehendale HM, Rogers JM, Shad AT, Skalko RG, Stanek EJ (2007) NTP-CERHR Expert Panel Report on the Reproductive and Developmental Toxicity of Hydroxyurea. *Birth Defects Res B Dev Reprod Toxicol.* 80:259-366.
7. Bristol-Myers-Squibb. Droxia (hydroxyurea capsules, USP). Available at [http://packageinserts.bms.com/pi/pi\\_droxia.pdf](http://packageinserts.bms.com/pi/pi_droxia.pdf).
8. NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Hydroxyurea. Available at <http://cerhr.niehs.nih.gov/chemicals/hydroxyurea/HUmonograph20090401.pdf>

9. NIH Consensus Development Conference: Hydroxyurea Treatment for Sickle Cell Disease. Program, abstracts, webcast archive, and final statement available at <http://consensus.nih.gov/2008/sicklecellstatement.htm>.