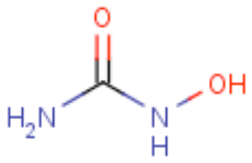
# NTP Testing Program Nomination: Hydroxyurea

## Background




Hydroxyurea was nominated by a private individual for carcinogenicity studies and by the National Institute of Environmental Health Sciences for toxicology studies based on critical data needs identified in the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR) Expert Panel Report on the Reproductive and Developmental Toxicity of Hydroxyurea (http://ntp.niehs.nih.gov/go/33220). Hydroxyurea is used chronically to treat sickle cell anemia and there is concern regarding safety associated with long-term use. The NTP CERHR Expert Panel identified numerous critical data needs that could be addressed by additional studies in human populations receiving hydroxyurea therapy. One critical data need identified was for 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, also called hydroxycarbamide, is marketed as Hydrea® and Droxia® by Bristol-Myers Squibb. Several FDA-approved unbranded (generic) hydroxyurea products are also available. Hydroxyurea is approved to treat sickle cell disease and certain cancers in adults. Numerous off-label uses are also reported including as a therapy for children with sickle cell disease. There are also active clinical investigations for other uses (http://clinicaltrials.gov/search/intervention=hydroxyurea). There are few if any effective alternative therapies for sickle cell disease and use of hydroxyurea in children appears to be increasing.

Hydroxyurea acts by inhibiting ribonucleotide reductase, leading to inhibition of DNA synthesis. It is considered an unequivocal genotoxicant but rigorous studies to evaluate carcinogenic potential have not been conducted. Overall, there is inadequate evidence for carcinogencity in humans or experimental animals, and the IARC considers hydroxyurea “not classifiable as to its carcinogenicity to humans (Group 3)”. However, the approved drug label contains a strong boxed warning for potential carcinogenic risk (http://www.fda.gov/cder/foi/label/2006/016295s039s036lbl.pdf). The NTP CERHR draft brief and expert panel report describe evidence for developmental and reproductive effects. Though there are few human studies, experimental animal studies demonstrate that hydroxyurea adversely affects development and the male reproductive tract.

Thus, there is potential developmental, reproductive, and carcinogenic hazard associated with hydroxyurea treatment. In a statement by an independent scientific panel following a recent NIH Consensus Development Conference, these (and other) risks were considered acceptable compared to the risks of untreated sickle cell disease. The panel statement also recommended further studies to provide more information about adverse developmental and reproductive effects and carcinogenic risk.

## Study Recommendations

No additional experimental animal toxicity studies are recommended at this time. Currently ongoing clinical trials, and additional prospective human studies that may be initiated in the future may address outstanding safety concerns associated with chronic hydroxyurea treatment. The NTP will monitor research progress in this area and if necessary, revisit the need for rodent toxicology studies.

## References and Supporting Documents


NTP CERHR Evaluation of Hydroxyurea:
Draft Brief and Final Expert Panel Report available at
http://cerhr.niehs.nih.gov/chemicals/hydroxyurea/hydroxyurea-eval.html

CERHR Final Expert Panel Report also published as:
Liebelt EL, Balk SJ, Faber W, Fisher JW, Hughes CL, Lanzkron SM, Lewis KM, Marchetti F, Mehendale HM, Rogers JM, Shad AT, Skalko RG, and Stanek EJ. 2007. NTP-CERHR expert panel report on the reproductive and developmental toxicity of hydroxyurea. Birth Defects Res B Dev Reprod Toxicol. 80(4):259-366. PMID: 17712860.

NIH Consensus Development Conference: Hydroxyurea Treatment for Sickle Cell Disease. Program, abstracts, webcast archive, and final statement available at
http://consensus.nih.gov/2008/2008SickleCellCDC119main.htm.

Final statement also published as:
Brawley OW, Cornelius LJ, Edwards LR, Gamble VN, Green BL, Inturrisi C, James AH, Laraque D, Mendez M, Montoya CJ, Pollock BH, Robinson L, Scholnik AP, and Schori M. 2008. National Institutes of Health Consensus Development Conference statement: hydroxyurea treatment for sickle cell disease. Ann Intern Med. 148(12):932-8. PMID: 18458271.

AHRQ Evidence Report:
Segal JB, Strouse JJ, Beach MC, Haywood C, Witkop C, Park HS, Wilson RF, Bass EB, Lanzkron S. Hydroxyurea for the Treatment of Sickle Cell Disease. Evidence Report/Technology Assessment No. 165. (Prepared by Johns Hopkins University Evidence-based Practice Center under contract No. 290-02-0018). AHRQ Publication No. 08-E007. Rockville, MD. Agency for Healthcare Research and Quality. February 2008. Available at
http://www.ahrq.gov/clinic/tp/hydscdtp.htm.

Also published as:
Lanzkron S, Strouse JJ, Wilson R, Beach MC, Haywood C, Park H, Witkop C, Bass EB, and Segal JB. 2008. Systematic review: Hydroxyurea for the treatment of adults with sickle cell disease. Ann Intern Med. 148(12):939-55. PMID: 18458272.

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 76: Some antiviral and antineoplastic drugs, and other pharmaceutical agents. Available at
http://monographs.iarc.fr/eng/monographs/vol76/index.php.