DRAFT
NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Hydroxyurea

Preface

The National Toxicology Program (NTP)[1] established the NTP Center for the Evaluation of Risks to Human Reproduction (CERHR) in June 1998. The purpose of the CERHR is to provide timely, unbiased, scientifically sound evaluations of the potential for adverse effects on reproduction or development resulting from human exposures to substances in the environment. The NTP-CERHR is headquartered at the National Institute of Environmental Health Sciences (NIEHS) and Dr. Michael Shelby is the director.[2]

CERHR broadly solicits nominations of chemicals for evaluation from the public and private sectors. Chemicals are selected for evaluation based upon several factors including the following:

- potential for human exposure from use and occurrence in the environment
- extent of public concern
- production volume
- extent of database on reproductive and developmental toxicity studies

CERHR follows a formal process for review and evaluation of nominated chemicals that includes multiple opportunities for public comment. Briefly, CERHR convenes a scientific expert panel that meets in a public forum to review, discuss, and evaluate the scientific literature on the selected chemical. CERHR expert panels use explicit guidelines to evaluate the scientific literature and prepare the expert panel reports. Public comment is invited prior to and during the meeting. The expert panel produces a report on the chemical's reproductive and developmental toxicities and provides its opinion of the degree to which exposure to the chemical is hazardous to humans. The panel also identifies areas of uncertainty and where additional data are needed. Expert panel reports are made public and comments are solicited.

Next, CERHR prepares the NTP Brief. The goal of the NTP Brief is to provide the public, as well as government health, regulatory, and research agencies, with the NTP's conclusions regarding the potential for the chemical to adversely affect human reproductive health or children's development. CERHR then prepares the NTP-CERHR Monograph, which includes the NTP Brief, the Expert Panel Report, and public comments on that report. The NTP-CERHR monograph is made publicly available on the CERHR web site and in hardcopy or CD from CERHR.

[1] NTP is an interagency program headquartered in Research Triangle Park, NC at the National Institute of Environmental Health Sciences, a component of the National Institutes of Health.

[2] Information about the CERHR is available on its web site (http://cerhr.niehs.nih.gov) or by contacting M.D. Shelby, Ph.D., Director, CERHR (P.O. Box 12233, MD EC-32, NIEHS, Research Triangle Park, NC 27709; telephone: 919-541-3455; facsimile: 919-316-4511; e-mail: shelby@niehs.nih.gov).

Abstract

The National Toxicology Program (NTP) Center for the Evaluation of Risks to Human Reproduction (CERHR) conducted an evaluation of the potential for hydroxyurea to cause adverse effects on reproduction and development in humans. Hydroxyurea is a drug used to treat cancer, sickle cell disease, and thalassemia. It is the only treatment for sickle cell disease in children, aside from blood transfusion and, in severe cases, bone marrow transplantation. Hydroxyurea is FDA-approved for reducing the frequency of painful crises and the need for blood transfusions in adults with sickle cell anemia who experience recurrent moderate to severe pain. Hydroxyurea is FDA-approved for use in adults with sickle cell anemia to reduce the frequency of painful crises and the need for blood transfusions. Hydroxyurea may be given to children and adults with sickle cell disease for an extended period of time or for repeated cycles of therapy. Treatment with hydroxyurea is associated with known side effects such as cytotoxicity and myelosuppression, and hydroxyurea can damage DNA (genotoxic).

CERHR selected hydroxyurea for evaluation because of: (1) its increasing use for treatment of sickle cell disease in children and adults, (2) knowledge that it inhibits DNA synthesis and is cytotoxic and (3) published evidence of reproductive and developmental toxicity in rodents.

The results of this evaluation are published in the NTP-CERHR Monograph on Hydroxyurea, which includes the NTP Brief on Hydroxyurea, the Expert Panel Report on the Reproductive and Developmental Toxicity of Hydroxyurea, and public comments on that report.

The NTP reached the following conclusions on the potential for exposure to hydroxyurea to cause adverse effects on human reproduction or development. The possible levels of concern, from lowest to highest, are negligible concern, minimal concern, some concern, concern, and serious concern.

- The NTP expresses serious concern that exposure of men to therapeutic doses of hydroxyurea may adversely affect sperm production. This level of concern is for all males who have reached puberty.

- The NTP concurs with the Expert Panel that there is concern that exposure of pregnant women to hydroxyurea may result in birth defects or abnormalities of fetal growth and postnatal development in their offspring.

- The NTP concurs with the Expert Panel that there is minimal concern that exposure of children to therapeutic doses of hydroxyurea at 5–15 years of age will adversely affect growth.

NTP will transmit the NTP-CERHR Monograph on Hydroxyurea to federal and state agencies, interested parties, and the public and make it available in electronic PDF format

on the CERHR web site < *http://cerhr.niehs.nih.gov* > and in printed text or CD from CERHR:

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Introduction

In October 2005, the CERHR Core Committee, an advisory committee composed of representatives from NTP member agencies, recommended hydroxyurea for expert panel evaluation. Hydroxyurea is a drug used to treat cancer, sickle cell disease, and thalassemia. It is the only treatment for sickle cell disease used in children, aside from blood transfusion and, in severe cases, bone marrow transplantation. Hydroxyurea is FDA-approved for use in adults with sickle cell anemia to reduce the frequency of moderate to severe painful crises and the need for blood transfusions. Treatment of children with sickle cell disease is currently an "off label" use of hydroxyurea. It may be given to children and adults with sickle cell disease for an extended period of time or for repeated cycles of therapy. Treatment with hydroxyurea is associated with known side effects including cytotoxicity (or toxicity to cells) and myelosuppression (or reduced production of red blood cells, white blood cells, and platelets), and hydroxyurea can damage DNA ("genotoxic").

CERHR selected hydroxyurea for expert panel evaluation because of (1) its increasing use for treatment of sickle cell disease in children and adults, (2) knowledge that it inhibits DNA synthesis and is cytotoxic, and (3) published evidence of reproductive and developmental toxicity in rodents. As part its evaluation, CERHR convened a panel of scientific experts (Appendix I) to review, discuss, and evaluate the scientific evidence on the potential reproductive and developmental toxicities of hydroxyurea. A public meeting of the NTP-CERHR Hydroxyurea Expert Panel was held on January 24–26, 2007, in Alexandria, VA.

The NTP-CERHR Monograph on Hydroxyurea includes the NTP Brief on Hydroxyurea, a list of the expert panel members (Appendix I), the Expert Panel Report on Hydroxyurea (Appendix II), and all public comments received on that report (Appendix III). The NTP-CERHR monograph is intended to serve as a single, collective resource on the potential reproductive and developmental effects of hydroxyurea. Those interested in reading this monograph may include individuals, members of public interest groups, staff of health and regulatory agencies and the medical and scientific communities.

The NTP Brief on Hydroxyurea presents the NTP's conclusions on the potential for hydroxyurea exposure to cause adverse reproductive or developmental effects in people. The NTP Brief is intended to provide clear, balanced, scientifically sound information. It is based on information provided in the expert panel report, public comments on that report, public and peer review comments on the draft NTP Brief, and additional scientific information published after the expert panel meeting.

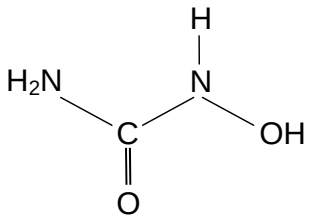
NTP Brief on Hydroxyurea

What is Hydroxyurea?

Hydroxyurea is a prescription medicine approved by the FDA for treatment of adults with certain types of cancer and sickle cell disease. Off-label uses include treatment for various myeloproliferative disorders (such as leukemia), thalassemia, psoriasis, HIV infection, and sickle-cell disease in children. It is the only treatment for sickle cell disease in children aside from blood transfusion and, in severe cases, bone marrow transplantation. Treatment with hydroxyurea in children and adults with sickle cell disease may occur for an extended period of time, sometimes for years and is associated with known side effects including cytotoxicity (i.e, toxicity to cells) and myelosuppression (i.e., suppression of bone marrow activity that results in reduced production of red blood cells, white blood cells, and platelets).

Sickle-cell disease can lead to painful vaso-occlusive crises where the sickle-shaped red blood cells obstruct capillaries and restrict blood flow to an organ or tissue, resulting in reduced blood supply, pain, and potential organ damage. Hydroxyurea is FDA-approved for use in adults with sickle cell anemia who experience moderate to severe crises (generally ≥ 3 in the previous 12 months) to reduce the frequency of these crises and the need for blood transfusions.

Figure 1. Hydroxyurea Chemical Structure



Hydroxyurea is a virtually tasteless, white crystalline powder with a chemical formula of $CH_4N_2O_2$ (Figure 1).

Although treatment of children with sickle cell disease is currently an off-label use of hydroxyurea, usage in children is reported frequently and appears to be increasing. Hydroxyurea is the preferred therapy among children with severe sickle cell anemia and their families compared to other therapeutic options (i.e., chronic red blood cell transfusion or bone marrow transplantation) (1). The National Heart, Lung, and Blood Institute of the National Institutes of Health is currently sponsoring a clinical trial to see if hydroxyurea is effective for preventing chronic end-organ damage in infants and children with sickle cell disease.

The mechanisms by which hydroxyurea relieves the symptoms of sickle cell disease are not completely understood. However, it is known that sickle cell disease is less severe in individuals who produce high levels of fetal hemoglobin (hemoglobin F).[3] For many patients, hydroxyurea increases the production of hemoglobin F which helps prevent the

[3] Hemoglobin is the iron-containing oxygen-transport protein found in red blood cells. Hemoglobin F is the main hemoglobin produced by the fetus in the second half of pregnancy. All adults produce small amounts of hemoglobin F.

formation of sickle-shaped red blood cells. In addition, hydroxyurea therapy can help prevent the vaso-occlusive crisis by improving movement of sickle-shaped red blood cells through the circulatory system.

Studies in cultured cells and animals show that hydroxyurea can damage DNA ("genotoxic"). It impairs the ability of cells to replicate DNA during the synthesis phase (S-phase) of the cell cycle. This impairment of cell division is the primary basis for its use in cancer chemotherapy.

Hydroxyurea, also commonly referred to as hydroxycarbamide, is marketed under the names Hydrea® and Droxia® by Bristol-Myers Squibb. Companies that are FDA-approved to manufacture unbranded (generic) hydroxyurea include Barr Pharmaceuticals, Duramed Pharmaceuticals, Par Pharmaceuticals, and Roxane Laboratories. Information on the production volume of hydroxyurea in the United States is not available.

How Are People Exposed to Hydroxyurea?

People are exposed to hydroxyurea through prescribed medication. Recommended doses of hydroxyurea for adults range from 15–35 mg/kg bw/day depending on the specific disease and the patient's response to treatment. In children, starting doses of 10–20 mg/kg bw/day and maximum doses of 25–35 mg/kg bw/day have been reported. Although not approved by the FDA, the use of hydroxyurea in children has been reported frequently and appears to be increasing.

Hydroxyurea is not recommended for use during pregnancy because of concern for effects on the fetus. However, fetuses may be exposed if women conceive while on therapy. It is not known how many pregnant or nursing women are exposed to hydroxyurea. Hydroxyurea crosses the placenta and is found in breast milk. Thus, taking hydroxyurea during pregnancy or lactation exposes the unborn child or infant to this drug.

No information is available on occupational exposures associated with the manufacture, packaging, or distribution of hydroxyurea in the United States although it has been detected in the air in some European pharmaceutical workplaces (2). No information is available on the occurrence of hydroxyurea in the environment.

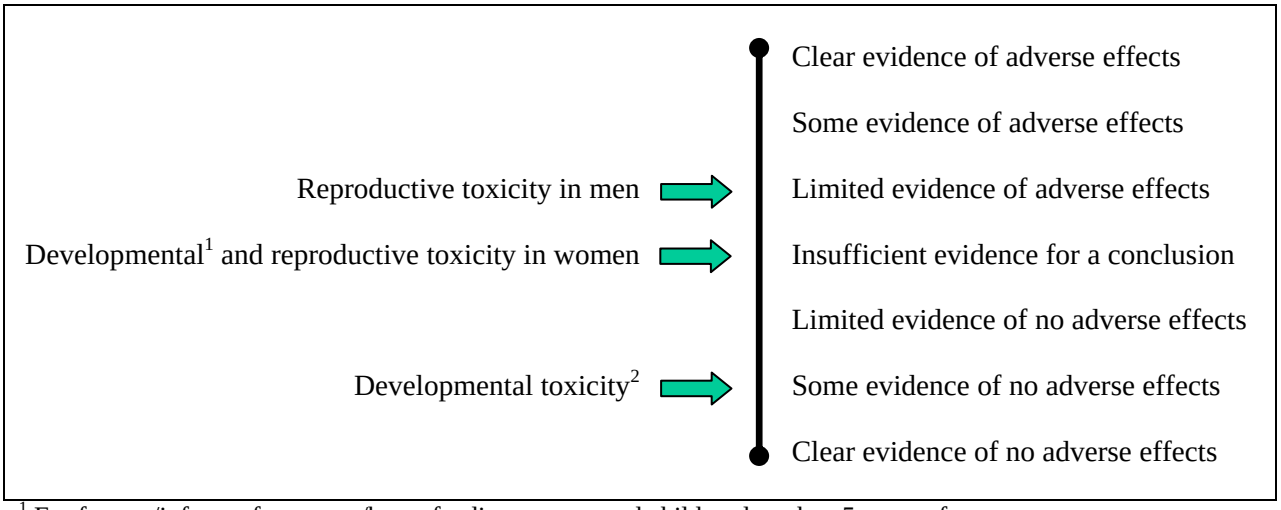
Can Hydroxyurea Affect Human Development or Reproduction?[4]

Probably. In humans, there is no direct evidence that exposure to hydroxyurea adversely affects development and there are only limited indications of impaired reproductive function (decreased sperm count in some patients) (see Figure 2a). However, studies in laboratory animals show that exposure to hydroxyurea can cause adverse effects on development and on the male reproductive tract (**see Figure 2b**). In laboratory rodents,

[4] Answers to this and subsequent questions may be: *Yes, Probably, Possibly, Probably Not, No or Unknown*

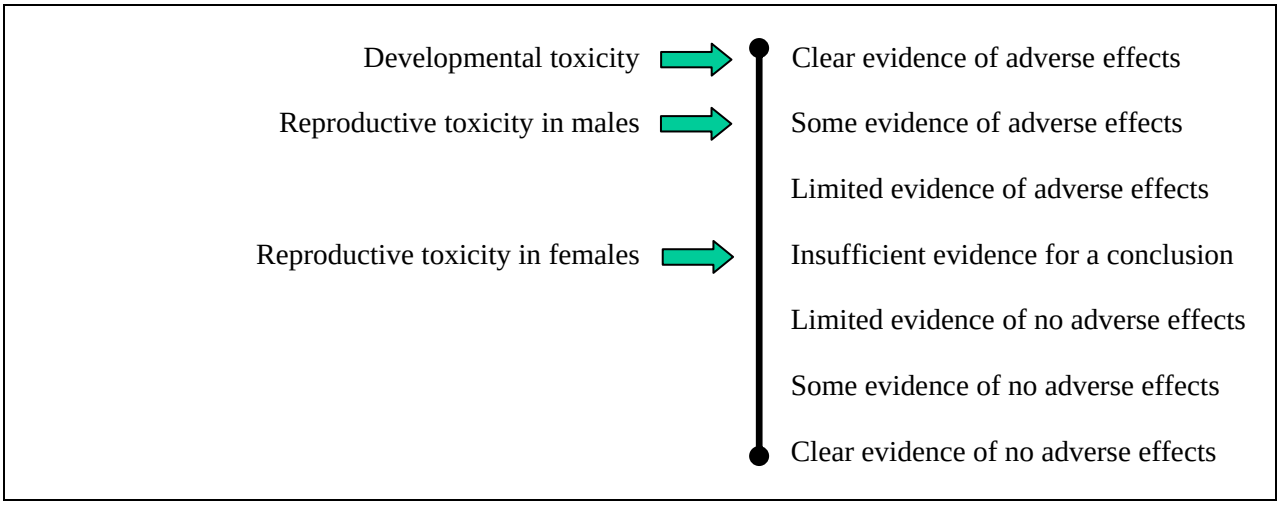
hydroxyurea produces birth defects, reduced numbers of live births, and abnormalities of fetal growth. In addition, experimental animal data show decreased testis weight and histologic abnormalities of seminiferous tubules in rats and mice, and decreased sperm counts in mice. The blood concentrations associated with some of these effects in laboratory animal studies are estimated to be similar to those achieved in patients on therapy (Table 1).

Figure 2a. The weight of evidence that hydroxyurea causes adverse developmental or reproductive effects in humans.



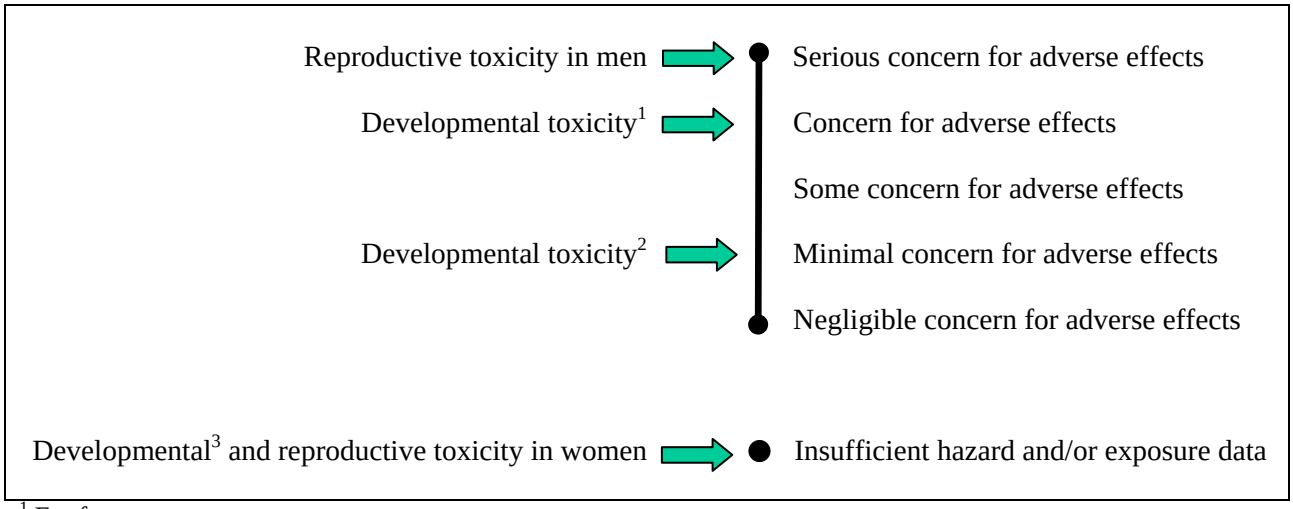
[1] For fetuses/infants of pregnant/breastfeeding women and children less than 5 years of age
[2] For children ages 5 to 15 years (based on growth assessments)

Figure 2b. The weight of evidence that hydroxyurea causes adverse developmental or reproductive effects in laboratory animals.



Scientific decisions concerning health risks are generally based on what is known as the "weight-of-evidence." In this case, the NTP recognizes the lack of sufficient data on the effects of hydroxyurea in humans and the clear evidence of adverse effects in laboratory animals and judges the scientific evidence sufficient to conclude that hydroxyurea may adversely affect human development and reproduction if exposures are sufficiently high (see **Figure 3**). The NTP recognizes that hydroxyurea is used to treat serious illnesses and that the decision to use hydroxyurea is made by the patient and his or her clinician.[5]

Figure 3. NTP conclusions regarding the possibilities that human development or reproduction might be adversely affected by exposure to hydroxyurea



[1] For fetuses
[2] For growth and development in children 5-15 years of age
[3] For infants and children under 5 years of age

Supporting Evidence

The expert panel report provides additional details and citations regarding studies on the possible reproductive and developmental toxicity of hydroxyurea [see Appendix II or (3)]. The expert panel evaluated several case reports and case series that described outcomes in a total of 58 pregnancies for 57 women exposed to hydroxyurea during gestation. One incidence of fetal death and several cases of minor malformations or reduced growth were reported, but the expert panel determined there was insufficient evidence to conclude that hydroxyurea causes or does not cause developmental toxicity when exposure occurs prenatally or during lactation (3). The panel noted that hydroxyurea is used to treat serious illnesses during pregnancy, such as sickle cell disease and essential thrombocythemia, which can themselves affect pregnancy outcome. For this reason, it is difficult to separate hydroxyurea-induced adverse effects from those resulting from the disease itself. Several studies have evaluated growth (height and weight) and

[5]The NTP recognizes that some states require involvement of parents in reproductive health-related decisions affecting minor children.

delays in development, such as onset of puberty, in children aged 5 to 15 years old. Although no growth or pubertal effects were reported in these studies, the panel noted that the durations of follow-up were relatively short, ranging from 6 months to 12 years. There were insufficient data for the panel to evaluate possible growth effects in children less than 5 years of age. Data were also not available on the long-term health effects, including abnormal development, impaired reproductive function, and risk of cancer, of fetal, childhood, or adolescent exposure to hydroxyurea.

There were sufficient experimental animal data available for the expert panel to conclude that hydroxyurea is a developmental toxicant following both oral and intraperitoneal routes of administration (4-6). In rats, hydroxyurea caused malformations, decreased fetal weight, and a decrease in the number of live pups at oral doses of 200 mg/kg bw/day during days 7 to 20 of gestation or ~300 mg/kg bw/day during days 6 to 15 of gestation. Increases in malformations of the eye and head and altered behavior were observed at a lower administered dose when rats were exposed to hydroxyurea by intraperitoneal injection (100 mg/kg bw/day from gestational days 9-12). Similarly, hydroxyurea caused malformations, decreased body weight, increased resorptions and stillbirths in mice when dams were treated orally with 200 mg/kg bw/day during days 6 to 17 of gestation. The malformations most commonly reported in rats and mice are neural tube defects, cleft palate, vertebral abnormalities, and deformities of the toes, such as polydactyly (extra digits), oligodactyly/adactyly (missing digits), syndactyly (webbed digits) or ectrodactyly ("lobster claw" syndrome). Mechanistic studies in rodents suggest the developmental toxicity of hydroxyurea relates to its ability to inhibit DNA synthesis with consequent arrest of the cell cycle and cell death.

The data were insufficient for the expert panel to evaluate the long-term effects of hydroxyurea in experimental animals exposed during gestation or as immature animals.

In reaching conclusions about developmental effects of hydroxyurea, the NTP considered how the doses used in the laboratory studies relate to human exposures (see Table 1). Blood levels of hydroxyurea in people taking this medication are similar to blood levels in mice administered a dose of hydroxyurea, 100 mg/kg, that is associated with adverse developmental effects (malformations of the eye and head and altered reflex response and behavior) (7-9). The NTP compared measured peak plasma concentrations in mice treated intraperitoneally with 100 mg/kg hydroxyurea to peak plasma concentrations in humans following oral administration of clinically relevant doses of hydroxyurea (3,10). Measured peak plasma concentration in mice at this dose was 111 mg/kg in nude mice and 175 mg/kg in C57/B6 mice (8,9), which is approximately 2.1 to 8.3 times higher than peak plasma concentrations in humans following treatment with 25 or 29 mg/kg hydroxyurea. i.e., 21-54 mg/L in adults with sickle-cell disease (11) and 48-52 mg/L in healthy adults (12,13). In addition, data from rat and monkey studies (3) indicate that hydroxyurea is eliminated more slowly from the embryo compared to the mother and that concentrations of hydroxyurea in the embryo exceed concentrations in maternal plasma shortly after exposure. Finally, estimates based on a pharmacokinetic model show the same average concentration of hydroxyurea in rat embryos whose mothers were dosed with 100 mg/kg bw/day during gestation as human embryos whose mothers took 10

mg/kg bw/day (69 mg-hour/L) (3). Although the assumptions and conclusions of this model need to be verified before it can be applied to risk prediction, it supports NTP's concern for hydroxyurea usage during pregnancy.

Table 1. Comparisons of Hydroxyurea Plasma Concentrations in Mice and Humans

Dose (mg/kg)	Animal Model/Population	C_{max} or "peak" concentration (mg /L)	Reference
Adverse effect doses			
100 (intraperitoneal)	mouse (nude)	111[b]	(9)
Developmental toxicity [a]	mouse (C57/B6)	175	(8)
50 (intraperitoneal) Reproductive toxicity [a]	mouse (C57/B6)	74	(8)
Therapeutically relevant doses [c]			
29 (oral)	human (healthy men, n=24-30)	48–51.9	(12,13)
25 (oral)	human (men and women with sickle-cell disease, n=6)	21–54	(11)
20 (oral; range 15-35)	human (men and women with sickle-cell disease, n=6)	26.5	(32)
22 (oral; range 14-37)	human (girls and boys with sickle-cell disease, n=11)	24.5	(32)
15 (oral)	human (men and women with sickle-cell disease and normal renal function, n=7)	28.3	(33)
	human (men and women with sickle-cell disease and mild to severe renal impairment, n=2-3 per category)	22.0–28.8	(33)

[a] Developmental toxicity is based on increased external malformations and altered behavior in rats (7) and reproductive toxicity is based on decreased testis weight and altered distribution of testicular germ cells in mice (17).

[b] The C_{max} following administration of 100 mg/kg was 1465 μM (111 μg/ml).

[c] Recommended starting doses of 10-20 mg/kg bw/day and maximum doses of 25-35 mg/kg bw/day have been used with adults and children with sickle cell disease and higher doses are recommended for treating solid tumors.

Although some clinical reports of impaired reproductive function in adult men are available, no studies with sufficient sample size were available to the expert panel to evaluate possible reproductive effects of hydroxyurea in people treated during childhood, adolescence, and/or adulthood. A clinical report reviewed by the expert panel presented the case of a 27-year old man with a sperm count of zero (azoospermia) after 6-months of hydroxyurea treatment. Prior to beginning hydroxyurea treatment his sperm count was normal (88 million/ml) and rebounded to a low-normal concentration (35 million/ml) within a year of discontinuing hydroxyurea treatment. This study was not considered useful for the expert panel evaluation because of the extremely small sample size (i.e., only one individual). However, subsequent to the expert panel meeting, two additional studies were published that presented case reports where hydroxyurea appeared to inhibit spermatogenesis in some male patients. In one study, a 35-year old man on hydroxyurea treatment for 3 years was diagnosed with infertility and azoospermia. Within 6 months of stopping hydroxyurea, the patient's sperm levels returned to normal and his wife conceived (14). In another study, a 27-year old man was azoospermatic during hydroxyurea treatment but had low-normal sperm count (30 million/ml) following cessation of hydroxyurea for 3 months. He again became azoospermatic when hydroxyurea treatment was re-initiated. Another patient did not show a decrease in sperm count while taking hydroxyurea (26 million/ml during treatment and 15 million/ml after ending treatment) (15). Thus, while some of the case reports support experimental animal data in mice of decreased sperm counts (16), it appears there may be considerable variation in responses among men. Detecting the impacts of hydroxyurea on human sperm count and function is complicated because sperm abnormalities are associated with untreated sickle cell disease. Inhibition of DNA synthesis and cell cycle arrest by hydroxyurea offers a possible mechanism for its impact on sperm counts.

The available experimental animal data are too limited to completely evaluate the effects of hydroxyurea on fertility and reproduction, especially for females. The existing data show that hydroxyurea produces reproductive toxicity in male rats at ~400–460 mg/kg bw/day in drinking water for 70–90 days as manifested by reduced testis weight and histologic abnormalities of seminiferous tubules. In male mice, intraperitoneal (ip) injection of 50 mg/kg bw/day hydroxyurea for 5 days caused decreased testis weight and flow cytometric abnormalities in testicular germ cell distribution. In male mice, higher ip doses of 625 to 5000 mg/kg bw/day hydroxyurea decreases sperm count 38 to 79 percent.

In reaching conclusions about reproductive effects of hydroxyurea, the NTP considered how the doses used in the laboratory studies relate to human exposures (Table 1). Blood levels of hydroxyurea in people taking therapeutic doses are similar to or exceed blood levels in mice administered a dose of hydroxyurea, 50 mg/kg, that is associated with adverse reproductive effects (decreased testis weight and flow cytometric abnormalities in testicular germ cell distribution in mice) (8,9,17). This conclusion is primarily based comparing the measured peak plasma concentration in mice treated intraperitoneally with 50 mg/kg hydroxyurea to peak plasma concentrations in humans following oral administration of clinically relevant doses of hydroxyurea (Table 1). The measured peak plasma concentration in C57/B6 mice at 50 mg/kg (8) is approximately 1.4 to 3.5 times higher than peak plasma concentrations in humans following treatment with 25 or 29

mg/kg hydroxyurea. i.e., 74 mg/L versus 21-54 mg/L in adults with sickle-cell disease (11) and 48-52 mg/L in healthy adults (12,13).

Several additional studies involving hydroxyurea treatment in humans have been published subsequent to the expert panel review. However, these studies either did not assess or did not report information related to evaluating developmental or reproductive hazard of hydroxyurea (14,18-28). One study reported higher cognitive function (verbal comprehension, fluid reasoning, and general cognitive ability) in children on hydroxyurea compared to those not on hydroxyurea treatment, possibly due to improved blood and oxygen supply to the brain or decreased fatigue and illness (29). The NTP did not identify any additional developmental or reproductive animal toxicity studies published in the peer-reviewed literature subsequent to the expert panel evaluation.

Should Exposures to Hydroxyurea Cause Concern?

Yes. Clinical reports indicate that hydroxyurea can impair sperm production in some males. The NTP considers these reports of decreased sperm production in some men on hydroxyurea therapy to be consistent with the expert panel's determination from studies in laboratory animals that hydroxyurea causes decreased testis weight and sperm counts, as well as histologic abnormalities of seminiferous tubules. It is not known if the effects in laboratory animals resulted in impaired reproductive function because fertility was not assessed in these studies. Despite the magnitude of the effects on sperm count in mice, e.g., reductions of 38 to 79% for intraperitoneal doses ranging from 625 to 5000 mg/kg bw/day, it is not clear that fertility in these animals would have been impacted because sperm count decrements of ~80% do not necessarily lead to reductions in fertility in laboratory rodents. Laboratory rodents are generally considered to be hyperfertile compared to men; therefore, decreases in sperm counts that do not necessarily impair fertility in rodents may correspond to an adverse effect in humans (30). In addition, clinical reports of azoospermia and decreases in sperm count corresponding to periods of hydroxyurea usage (and rebounding to normal levels during discontinuation of treatment) suggest that, at least in some men, hydroxyurea can have significant effects on sperm count and adversely affect fertility. Blood levels of hydroxyurea in people taking this medication are similar to or exceed blood levels in mice administered a dose of hydroxyurea, 50 mg/kg, that is associated with a adverse reproductive effects (decreased testis weight and flow cytometric abnormalities in testicular germ cell distribution in mice) (8,9,17). In February 2008, the National Institutes of Health (NIH) sponsored a Consensus Development Conference on Hydroxyurea Treatment for Sickle Cell Disease. The draft consensus statement issued by the independent panel of scientists recognized the possibility for temporary decreases in sperm counts or sperm abnormalities as a side-effect of treatment. They concluded that the risks of such effects in adults are acceptable compared to the risk of untreated sickle cell disease (31). Fertility management options for men can include (1) banking sperm prior to treatment, (2) annual monitoring of sperm counts, and (3) use of contraception during therapy and for at least 3 months after ending treatment (15). Data are not sufficient in humans or experimental animals to evaluate possible reproductive effects in women on hydroxyurea therapy.

Hydroxyurea is not recommended for use during pregnancy (31). However, fetuses may be exposed if women conceive while on hydroxyurea therapy. Although sufficient data are not available to determine if exposure to hydroxyurea during pregnancy adversely affects the human fetus, animal data from multiple species indicate that hydroxyurea produces malformations, reduced number of live births, and abnormalities in fetal growth. Blood levels of hydroxyurea in people taking this medication are similar to blood levels in mice administered a dose of hydroxyurea, 100 mg/kg, that is associated with adverse developmental effects in rats (malformations of the eye and head and altered reflex response and behavior) (7-9).

There is no evidence from the existing studies that hydroxyurea treatment at therapeutic doses affects growth or development (i.e., pubertal progression) in children age 5–15 years. However, data are not sufficient to evaluate possible effects on growth and development in infants and children younger than 5 years.

NTP Conclusions[6]

The NTP expresses serious concern that exposure of men to therapeutic doses of hydroxyurea may adversely affect sperm production. This level of concern is for all males who have reached puberty.

This level of concern is higher than that expressed by the Expert Panel and is based on (1) experimental animal data showing decreased testis weight and sperm count, as well as cellular effects on the testes, and (2) additional clinical reports of decreased or zero sperm count in men undergoing hydroxyurea therapy. These reports were not published when the Expert Panel completed its deliberations. Blood levels of hydroxyurea in people taking this medication are similar to blood levels in laboratory animals administered a dose of hydroxyurea that is associated with adverse reproductive effects. The "serious concern" expressed by the NTP for effects on sperm production does not necessarily conflict with conclusions reached by other scientists or panels who have concluded that such risks are acceptable compared to the risk of untreated sickle cell disease. The NTP recognizes that hydroxyurea is used to treat serious illnesses and that the decision to use hydroxyurea by a man of reproductive age is made by the patient and his clinician. Fertility management options for men can include (1) banking sperm prior to treatment, (2) annual monitoring of sperm counts, and (3) use of contraception during therapy and for at least 3 months after ending treatment.

The NTP concurs with the Expert Panel that there is concern that exposure of pregnant women to hydroxyurea may result in birth defects or abnormalities of fetal growth and postnatal development in their offspring.

This conclusion is based on data from animal studies showing that hydroxyurea produces birth defects, reduced number of live births, and abnormalities of fetal growth in multiple

[6] Note that the possible levels of concern, from lowest to highest, are negligible concern, minimal concern, some concern, concern, and serious concern.

laboratory animal species. Blood levels of hydroxyurea in people taking this medication are similar to blood levels in laboratory animals administered a dose of hydroxyurea that is associated with adverse developmental effects. The current advice for women who are trying to become pregnant or become pregnant while taking hydroxyrea is to stop taking the drug. The NTP recognizes that hydroxyurea is used to treat serious illnesses and that the decision to use hydroxyurea by a woman of reproductive age or by a pregnant woman is made by the patient and her clinician.

The NTP concurs with the Expert Panel that there is minimal concern that exposure of children to therapeutic doses of hydroxyurea at 5–15 years of age will adversely affect growth.

This conclusion is based on human studies reporting no adverse effects on growth (height and weight) or development (i.e., onset of puberty). However, the absence of studies on the long-term health effects, including effects on reproductive function and risk of cancer, following childhood exposures to hydroxyurea support expressing "minimal" concern as opposed to "negligible" concern. In addition, there are no data on growth effects in children less than 5 years of age. As noted above, there is serious concern for effects on spermatogenesis in all males who have reached puberty.

These conclusions are based on the information available at the time this brief was prepared. As new information on toxicity and exposure accumulates, it may form the basis for either lowering or raising the levels of concern expressed in the conclusions.

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6. High quality data on the pharmacokinetics of hydroxyurea following oral administration do not appear to be available for rodents. The expert panel considered intraperitoneal and oral routes of administration as equally relevant during the evaluation due to similar pharmacokinetics. This is primarily based on the finding that in mice similar amounts of hydroxyurea are excreted in the urine (~90%) within 24-hours following either oral or intraperitoneal dosing with 200 mg/kg (4). Slightly less is excreted at a higher intraperitoneal dose of 500 mg/kg (82-88%). The NTP notes greater differences in 24-hour urinary excretion in rats based on route of administration (57% following oral dosing of 50 mg/kg and 90% after intraperitoneal administration of 100 mg/kg) (4). The NTP would have more confidence in the comparability of the oral and intraperitoneal routes of administration in rodents if well-designed pharmacokinetic studies for oral administration were available. In humans, oral and intravenous administration of hydroxyurea produces similar pharmacokinetic profiles suggesting minimal impact of first-pass metabolism following oral delivery (5).
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10. The NTP considers it appropriate to use a mouse pharmacokinetic study to estimate blood levels in the rat developmental toxicity study because (1) both studies used an intraperitoneal route of administration, and (2) the rat and mouse excrete similar amounts hydroxyurea in urine (24-hour urinary excretion of ~90% following intraperitoneal administration of 200 mg/kg in mice and 100 mg/kg in

rats) and have similar half-lives of 11-15 minutes following intraperitoneal dosing with 100 mg/kg (3, 4). Comparisons based on both the peak and daily (i.e., "area under the curve") concentrations would be considered appropriate because it is not known which measure accounts for the reported effects of hydroxyurea on the fetus. However, the two key mouse pharmacokinetic studies have significantly different AUC values (24 versus 7,131 mg-minute/L over a period of two hours) despite having similar peak concentrations (111 versus 175 mg/L) and half-life estimates (0.18 versus 0.27 hour) (8, 9). The basis for the different AUC values is unclear. For this reason, the peak concentration values are considered more reliable as a basis for comparing circulating concentrations in rodents and humans.

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Appendix I. NTP-CERHR Hydroxyurea Expert Panel

A 13-member panel of scientists covering disciplines such as toxicology, epidemiology, and medicine was recommended by the CERHR Core Committee and approved by the Associate Director of the National Toxicology Program. Prior to the expert panel meeting, the panelists critically reviewed articles from the scientific literature, as well as a variety of other relevant documents. Based on this material, they identified key studies and issues for discussion. At a public meeting held January 24–26, 2007, the expert panel discussed these studies, the adequacy of available data, and identified data needed to improve future assessments. The expert panel reached conclusions on whether exposure to hydroxyurea might result in adverse effects on human reproduction or development. Panel conclusions were based on the scientific evidence available at the time of the public meeting. The NTP-CERHR released the final expert panel report for public comment on March 5, 2007 and the deadline for public comments was April 18, 2007 (*Federal Register Vol. 72:8384–8385, 2007*). The expert panel report on hydroxyurea is provided in Appendix II and the public comments received on the report are in Appendix III. The expert panel report on hydroxyurea is also available on the CERHR website (http://cerhr.niehs.nih.gov).

NTP-CERHR Hydroxyurea Expert Panel

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Jeffrey Fisher, Ph.D. University of Georgia Athens, GA	Aziza Shad, M.D. Georgetown University Washington, DC
Claude Hughes, Jr., M.D., Ph.D. RTI International Research Triangle Park, NC	Richard Skalko, Ph.D. East Tennessee State University Johnson City, TN
Sophie Lanzkron, M.D. Johns Hopkins University Baltimore, MD	Edward Stanek III, Ph.D. University of Massachusetts Amherst, MA
Kerry Lewis, M.D. Howard University Washington, DC	