



**National Toxicology Program**

U.S. Department of Health and Human Services

## **Draft Report on Carcinogens Concept**

*Helicobacter pylori:*

### **Chronic Infection**

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## Rationale and public health significance

More than half of the world's population is infected with *Helicobacter pylori* (*H. pylori*), a bacterium that colonizes the luminal mucosal surface of the stomach and causes peptic ulcers in humans (Krueger *et al.* 2015, Testerman and Morris 2015). The International Agency for Cancer on Research (IARC 2012) has classified chronic infection of this infectious agent as carcinogenic to humans (Group 1) based on epidemiological studies finding increased risks of non-cardia gastric cancer and low-grade mucosa-associated lymphoid tissue (MALT) gastric lymphoma (IARC 2012) among *H. pylori* infected people. Moreover, *H. pylori* is regarded to be a major contributor to the global burden of cancer (~6.2% of all cancers) (Plummer *et al.* 2015) and is the major target of global strategies to prevent gastric cancer (Herrero *et al.* 2014). As IARC cancer assessments are the outcome of a peer-reviewed process (<http://monographs.iarc.fr/ENG/Preamble/Preamble-IntReport.pdf>) and the carcinogenicity of *H. pylori* is well established, National Toxicology Program (NTP) plans to evaluate *H. pylori* for potentially listing in the Report on Carcinogens (RoC) by applying the RoC listing criteria to the IARC assessments of the evidence of carcinogenicity from studies in humans, experimental animals, and mechanisms.

Globally, strategies for preventing *H. pylori* associated gastric cancer are being actively explored (Herrero *et al.* 2014). This primarily involves a series of clinical trials and analysis activities to evaluate the effectiveness of programs to screen and treat (e.g., antibiotics) infected individuals in populations varying by gastric cancer risk or *H. pylori* prevalence. In the United States and elsewhere, *H. pylori* infection disproportionately affects minorities, low-income populations, and certain immigrants groups who may benefit from these interventions. As publication of the RoC usually garners media and public interest in the United States, a listing of *H. pylori* in the report may raise awareness and support ongoing efforts of cancer prevention.

## 1 Background

*H. pylori* is a gram negative, multi-flagellated bacterium that has infected humans for more than 58,000 years. It colonizes the luminal mucosal surface of the antrum and body (corpus) of the stomach; if untreated, the infection usually lasts for the life of an individual (Testerman and Morris 2014). Humans can be infected by multiple strains that are heterogeneous with respect to genotype and phenotype and adaptable to changing environments, which may explain their ability to escape the host-immune system and become resistant to antibiotics (IARC 2012). All *H. pylori* strains express urease, which converts urea to ammonia and carbon dioxide, raising the pH of the surrounding area. A neutral pH environment, found in the mucosal layer adjacent to the gastric surface epithelium, is needed for the bacterium's growth (Testerman and Morris 2014). The *H. pylori* genome codes for several virulence factors, such as cytotoxin-associated gene A product (CagA) and vacuolating cytotoxin (VacA), and these factors vary geographically and across strains.

### ***1.1 Human exposure***

*H. pylori* is a common infection that affects ~ 50% of the adult population worldwide with substantial variation in infection rates within and between countries. In general, infection is more common in lower income countries (3% to 10% incidence, 80% prevalence) than economically developed countries (0.5% incidence, 20% to 50% prevalence) (Malnick *et al.* 2014, Rosenberg *et al.* 2010). Age-adjusted prevalence rates are particularly high in parts of Asia, Central/South America, and Africa (Roberts *et al.* 2016, Peleteiro *et al.* 2014, IARC 2012). In the United States, ~30% of people are infected with *H. pylori* (based on NHANES 1999 to 2000 data) with the highest prevalence rates found among minority groups (e.g., Hispanics 45% and African Americans 42%) and immigrants from Asia and other high risk countries. Moreover, minorities may have a higher prevalence of more virulent strains; for example, African-Americans had a higher risk of CagA positive infection than whites in a study of mostly low-income individuals living in southeastern United States (Epplein *et al.* 2011). Risk factors for *H. pylori* infection include age, race, socioeconomic status (low family income and lower education level), and crowded housing (Krueger *et al.* 2015). Other risk factors identified using NHANES data are soil-related occupations among adults and the use of well water among people 3 to 19 years old (Krueger *et al.* 2015).

The prevalence of *H. pylori* infection increases with increasing age (Krueger *et al.* 2015). In lower-income countries, initial infection often occurs in early childhood and prevalence rates peak by 50 years of age. In economically developed countries, infection is more common in adulthood with peak incidence among those older than 60 years of age (Malnick *et al.* 2014). The bacterium is spread by person-to-person contact especially among family members. Routes of transmission include oral-oral, fecal-oral, iatrogenic, and possibly from contaminated water (IARC 2012, Bui *et al.* 2016). *H. pylori* has been detected in surface and ground water in the United States (IARC 2012) and the U.S. EPA considers it a candidate contaminant substance for possible regulatory action under the Safe Drinking Water Act (Krueger *et al.* 2015).

### ***1.2 Concerns for carcinogenicity and other health outcomes***

The carcinogenicity of *H. pylori* is well established (Plummer *et al.* 2015). Two IARC working groups (reported in 1994 and 2012 monographs) concluded that chronic infection of *H. pylori* is carcinogenic to humans (Group 1) based on sufficient evidence from epidemiological studies finding a casual association between chronic infection of *H. pylori* and increased risks of non-cardia gastric cancer (region of the stomach distal to the cardia) and MALT gastric lymphoma. The evaluation of non-cardia gastric cancer was primarily based on 16 nested case-control studies, a pooled analysis of 12 of these studies including over 750 cases (overall ~3-fold increased risk with risks in individual studies ranging from 1.5 to 11) (Helicobacter and Cancer Collaborative Group 2001), 6 cohort studies (2- to 3-fold increased risks), and 4 meta-analyses. A smaller database was available for MALT gastric lymphoma consisting of a nested case-control study, a case-control study, and 16 intervention studies, which found that eradication of *H. pylori* infection in MALT gastric lymphoma patients caused complete remission of the cancer. IARC concluded that there is evidence suggesting a lack of carcinogenicity of chronic infection of *H. pylori* and esophageal adenocarcinoma and considered the evidence for

other cancers inadequate because of conflicting results across studies, limitations or biases in the study design, or few studies for each cancer site.

IARC also concluded that there is sufficient evidence for the carcinogenicity of infection with *H. pylori* from studies in experimental animals. Importantly, similar types of cancer were observed in animal models of *H. pylori* infection as those linked with infection in humans: gastric tumors in gerbils (which may depend on the strain of gerbils and/or *H. pylori*) and transgenic mice and MALT gastric lymphoma in mice.

Mechanistic data provide insight on the nature of the cancer hazard (e.g., chronic infection, susceptibility), its plausibility, and coherence. *H. pylori* gastric carcinogenesis starts with gastritis and is associated with inflammatory infiltrates of neutrophils, lymphocytes, and plasma cells, leading to chronic inflammation, followed by oxidative stress and gastric atrophy. This results in cellular turnover/proliferation of progenitor cells in conjunction with changes in gene expression, methylation, and mutation, followed by progression to intestinal metaplasia, dysplasia, and adenocarcinoma (IARC 2012, Siao and Somsouk 2014, Testerman and Morris 2014). IARC proposed that *H. pylori*-induced inflammation is influenced by host modulation of immune response (which may be due in part to genetic polymorphisms), virulence factors (e.g., CagA and VacA outer inflammatory protein, OipA), and altered gastric secretory function. The virulence of *H. pylori* strains varies geographically and may help explain geographical patterns of gastric cancer risk (Yamaoka *et al.* 2010). In human cancer studies, odds ratios were higher for CagA-positive *H. pylori* infection than for CagA-negative infection. Collectively, this information may help explain why only a small fraction of *H. pylori* infected individuals develop gastric cancer.

In 2005, the Nobel Prize in Physiology or Medicine was granted to Barry Marshal and Robin Warren for their discovery that an infectious agent, *H. pylori*, causes gastritis and peptic ulcers (up to 80% of gastric ulcers and greater than 90% of duodenal ulcers) ([http://www.nobelprize.org/nobel\\_prizes/medicine/laureates/2005/press.html](http://www.nobelprize.org/nobel_prizes/medicine/laureates/2005/press.html)). *H. pylori* infection is also associated with non-ulcer dyspepsia and some extragastric diseases such as iron deficiency anemia and immune thrombocytopenia purpura (Testerman and Morris 2014).

### ***1.3 Current question: How to prevent gastric cancer?***

Gastric cancer is the third leading cause of cancer deaths worldwide; the incidence and mortality are higher in men than women, and 70% of the cancer burden occurs in developing countries (Herrero *et al.* 2014). Although the United States is considered a low-risk country for gastric cancer, cancer incidence and mortality show racial disparity, with higher rates found among minorities (African-Americans, Hispanic, Asians, Alaska Natives) and immigrants (e.g., age-adjusted gastric cancer incidence among Korean men living in Los Angeles is 40 per 100,000) compared to non-Hispanic whites (<http://seer.cancer.gov/statfacts/html/stomach.html>, Epplen *et al.* 2011, Taylor *et al.* 2014, Keck *et al.* 2015, Jenks 2015).

The importance of *H. pylori* as the major risk factor (i.e., accounting for up to 80%) for non-cardia gastric cancer is well established in the scientific community (e.g., IARC

Working Groups, The III Working Group Consensus Report 2015, reported by Zagari *et al.* 2015, Park *et al.* 2013). This single agent is responsible for approximately 780,000 deaths worldwide, which represents 6.2% of all cancer deaths (Plummer *et al.* 2015). *H. pylori* infection is also thought to cause 92% to 98% of all MALT gastric lymphoma cases. The current question for the health community is not about causation, but whether *H. pylori* screening and eradication programs should be implemented and if so, how these prevention strategies should be carried out. With few exceptions in some high-risk countries, there are no public health programs for gastric cancer prevention (Herrero *et al.* 2014).

Randomized clinical studies have shown that treatment of *H. pylori* reduces gastric cancer risk by approximately 35% (Herrero *et al.* 2014, Areia *et al.* 2013, Park *et al.* 2013). The effectiveness of reducing cancer risk depends on the stage of *H. pylori* associated gastric disease; treatment before atrophic changes can eliminate cancer risk (Graham 2014, 2015). Several economic modeling studies have concluded that screening for *H. pylori* and treating identified cases to prevent gastric cancer is cost effective in both low- and high-risk countries (Herrero *et al.* 2014), although cost savings are greater in high-risk countries. Cost effectiveness also depends on age of screening and *H. pylori* prevalence. In the United States, cost per life savings was better among immigrant groups and minorities compared to whites (reviewed by Lansdorp-Vogelaar and Sharp 2013). However, there are some concerns that large-scale eradication programs could lead to increases in antimicrobial resistance or alter gut microflora. In addition, *H. pylori* may be protective of gastroesophageal reflux, Barrett esophagus, and esophageal adenocarcinoma (Herrero *et al.* 2014). Currently, no *H. pylori* vaccine is available, which would be expected to provide the greatest cost benefit when administered in infancy (Lu and Li 2014). A 2014 IARC Working Group (Section on Early Detection and Prevention) recommended that all countries identify subpopulations that would most likely benefit from intervention and explore the possibility of developing population-based screening programs. Randomized trials are currently being conducted in several countries that may help inform these decisions (Herrero *et al.* 2014).

## **2 Objective and approach for developing the RoC monograph**

The objective of the NTP evaluation is to review chronic infection of *H. pylori* for listing in the RoC using a strategy that takes advantage of the IARC assessment of cancer studies and other data relevant to the carcinogenicity of *H. pylori*.

In developing this concept, ORoC carried out several problem formulation activities, including reviewing the IARC monograph and searching the peer-reviewed literature to (1) determine the extent of U.S. exposure to *H. pylori* and (2) identify any potential controversies with IARC's assessment or publications of cancer studies published since the IARC review that are not consistent with findings from the earlier studies. Based on these preliminary literature searches, no information was identified that would argue against using the IARC assessment as the scientific body for applying the RoC listing criteria and reaching a listing recommendation. In addition, the current interest in cancer prevention strategies and the question on whether or not to implement large scale,

population-wide screening and treatment of *H. pylori* to prevent gastric cancer were identified.

The draft RoC monograph will consist of (1) a cancer hazard evaluation component, (2) a substance profile, and (3) an appendix that provides information on cancer prevention. The cancer hazard evaluation will succinctly describe the process for how the preliminary listing recommendation and level of conclusions were reached. NTP will rely on IARC's assessment and peer review of the cancer studies in humans, experimental animals, and mechanistic and other relevant data, which has widespread consensus in the scientific and health professional communities (The III Working Group Consensus Report 2015, reported by Zagari *et al.* 2015, Park *et al.* 2013), and not conduct its own evaluation of the individual studies. For example, in reaching its preliminary level of evidence conclusion for the carcinogenicity of *H. pylori* from studies in humans, NTP would apply its criteria for sufficient/limited evidence to IARC assessment that chronic *H. pylori* infection is linked with an increased risk of non-cardia gastric cancer and MALT gastric lymphoma. Similarly, in reaching its level of evidence conclusion from studies in experimental animals, NTP would use IARC's conclusion that *H. pylori* infection increases tumor incidence (for the same types of neoplasms) in gerbils and/or mice to determine whether the evidence meets the RoC listing criterion for sufficient evidence of carcinogenicity.

The substance profile will summarize the carcinogenicity (e.g., humans, experimental animals, and mechanistic data) evidence that is key to NTP's listing recommendation and information about exposure. Carcinogenicity information will come largely from the cancer hazard evaluation published in the IARC monograph and exposure data will be updated for U.S.-specific information.

The IARC Working Group report, *Helicobacter pylori Eradication as a Strategy for Preventing Gastric Cancer*, will serve as the basis for the monograph appendix that summarizes cancer prevention strategies. The information will be supplemented with any new studies evaluating screening and eradication and expert or government recommendations or guidelines. Providing information on activities to reduce exposure is consistent with the spirit of the congressional mandate for the RoC (i.e., the report should discuss government regulations to limit exposure) and should facilitate hazard communication efforts when the RoC monograph and RoC are published.

### **3 Peer review of the draft RoC monograph**

Per the RoC process, OROc will release the draft RoC monograph on chronic infection to *H. pylori* for peer review. Similar to the peer review of other candidate substances, peer reviewers will be asked to comment on whether (1) there is evidence that a significant number of people residing in the United States are infected with *H. pylori* and (2) whether the carcinogenicity and mechanistic information in the substance profile is clear, objectively presented, and supports NTP's listing preliminary listing recommendation. They will also be asked whether there are any key issues or studies published since the

IARC monograph that may affect the listing recommendation and thus warrant an independent evaluation by NTP and update to the primary studies.

## References

1. [Areia M, Carvalho R, Cadime AT, Rocha Goncalves F, Dinis-Ribeiro M. 2013. Screening for gastric cancer and surveillance of premalignant lesions: a systematic review of cost-effectiveness studies. \*Helicobacter\* 18\(5\): 325-337.](#)
2. [Bui D, Brown HE, Harris RB, Oren E. 2016. Serologic evidence for fecal-oral transmission of \*Helicobacter pylori\*. \*Am J Trop Med Hyg\* 94\(1\): 82-88.](#)
3. [Graham DY. 2014. History of \*Helicobacter pylori\*, duodenal ulcer, gastric ulcer and gastric cancer. \*World J Gastroenterol\* 20\(18\): 5191-5204.](#)
4. [Graham DY. 2015. \*Helicobacter pylori\* update: gastric cancer, reliable therapy, and possible benefits. \*Gastroenterology\* 148\(4\): 719-731 e3.](#)
5. [Herrero R, Park JY, Forman D. 2014. The fight against gastric cancer - the IARC Working Group report. \*Best Pract Res Clin Gastroenterol\* 28\(6\): 1107-1114.](#)
6. [IARC. 1994. \*Helicobacter pylori\*. In \*Schistosomes, Liver Flukes and Helicobacter Pylori\*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 61. Lyon, France: International Agency for Research on Cancer. pp. 177-240.](#)
7. [IARC. 2012. \*Helicobacter pylori\*. In \*Biological Agents\*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 100B. Lyon, France: International Agency for Research on Cancer. pp. 365-435.](#)
8. [Jenks S. 2015. Renewed focus on preventing gastric cancer. \*J Natl Cancer Inst\* 107\(1\): 501.](#)
9. [Krueger WS, Hilborn ED, Converse RR, Wade TJ. 2015. Environmental risk factors associated with \*Helicobacter pylori\* seroprevalence in the United States: a cross-sectional analysis of NHANES data. \*Epidemiol Infect\* 143\(12\): 2520-2531.](#)
10. [Lansdorp-Vogelaar I, Sharp L. 2013. Cost-effectiveness of screening and treating \*Helicobacter pylori\* for gastric cancer prevention. \*Best Pract Res Clin Gastroenterol\* 27\(6\): 933-947.](#)
11. [Lu B, Li M. 2014. \*Helicobacter pylori\* eradication for preventing gastric cancer. \*World J Gastroenterol\* 20\(19\): 5660-5665.](#)
12. [Malnick SD, Melzer E, Attali M, Duek G, Yahav J. 2014. \*Helicobacter pylori\*: friend or foe? \*World J Gastroenterol\* 20\(27\): 8979-8985.](#)
13. [Park JY, Forman D, Greenberg ER, Herrero R. 2013. \*Helicobacter pylori\* eradication in the prevention of gastric cancer: are more trials needed? \*Curr Oncol Rep\* 15\(6\): 517-525.](#)
14. [Peleteiro B, Bastos A, Ferro A, Lunet N. 2014. Prevalence of \*Helicobacter pylori\* infection worldwide: a systematic review of studies with national coverage. \*Dig Dis Sci\* 59\(8\): 1698-1709.](#)

15. [Plummer M, Franceschi S, Vignat J, Forman D, de Martel C. 2015. Global burden of gastric cancer attributable to Helicobacter pylori. \*Int J Cancer\* 136\(2\): 487-490.](#)
16. [Roberts SE, Morrison-Rees S, Samuel DG, Thorne K, Akbari A, Williams JG. 2016. Review article: the prevalence of Helicobacter pylori and the incidence of gastric cancer across Europe. \*Aliment Pharmacol Ther\* 43\(3\): 334-345.](#)
17. [Rosenberg JJ. 2010. Helicobacter pylori. \*Pediatr Rev\* 31\(2\): 85-86; discussion 86.](#)
18. [Siao D, Somsouk M. 2014. Helicobacter pylori: evidence-based review with a focus on immigrant populations. \*J Gen Intern Med\* 29\(3\): 520-528.](#)
19. [Testerman TL, Morris J. 2014. Beyond the stomach: an updated view of Helicobacter pylori pathogenesis, diagnosis, and treatment. \*World J Gastroenterol\* 20\(36\): 12781-12808.](#)
20. [Yamaoka Y. 2010. Mechanisms of disease: Helicobacter pylori virulence factors. \*Nat Rev Gastroenterol Hepatol\* 7\(11\): 629-641.](#)