5. Summary of Data Reported and Evaluation

5.1 Exposure data

Helicobacter are spiral, flagellated, gram-negative bacteria that colonize the gastrointestinal tract of human beings and animals. *H. pylori* is restricted to human gastric mucosa and can infect some other primates. *H. pylori* strains are genetically heterogeneous, and this attribute is useful in studies of transmission. *H. pylori* can be cultured, is sensitive to most antibiotics *in vitro* and is characterized by very strong urease activity.

Colonization of the gastric mucosa and subsequent development of gastritis are dependent on bacterial factors, including motility, potent urease activity and specific adherence to gastric epithelium.

H. pylori can be detected in gastric biopsy specimens and indirectly by serology and analysis of breath after ingestion of labelled urea. Standard histological and bacteriological techniques, the polymerase chain reaction and indirect tests are highly sensitive. The rapid urease test on biopsy specimens is practical but less sensitive. Epidemiological studies currently involve use of serological tests and mainly commercially available enzyme-linked immunosorbent assay kits.

H. pylori occurs worldwide and causes a chronic infection which rarely resolves spontaneously. Its prevalence is highest in developing countries and increases rapidly during the first two decades of life, such that 80–90% of the population may be infected by early adulthood. In most developed countries, the prevalence of infection is substantially lower at all ages, and especially in childhood. The prevalence increases gradually throughout life up to the age of 70–80 years. The prevalence in both developed and developing countries is higher among people in lower socioeconomic classes and may be associated with crowding in childhood. A progressive reduction in the rate of infection early in life of people in successive birth cohorts has been observed in developed countries. Transmission occurs from one person to another; both oral–oral and oral–faecal routes have been postulated.

H. pylori causes gastritis in all infected people. This is accompanied by a specific, systemic immunoglobulin G response. Nevertheless, many such infections are asymptomatic. In some people, the infection gives rise to duodenal or gastric ulceration. The infection can be eradicated successfuly with several regimens in which different drugs are combined. Eradication of *H. pylori* resolves gastritis, prevents recurrence of peptic ulcer disease and leads to a significant decline in immunoglobulin response within six months.

5.2 Human carcinogenicity data

Six studies in which estimates of prevalence of infection by *H. pylori* were related to estimates of concurrent or earlier incidence of or mortality from cancer of the stomach in five or fewer populations show no consistent association between these variables. Significantly positive geographical correlations were observed, however, in two larger studies in which the ranges of cancer incidence and mortality were much wider: one in 46 rural populations in China and the other in 17 populations in Europe, Japan and the USA. The populations of

certain developing countries, including many in Africa and some in Asia, have low rates of gastric cancer; the prevalence of *H. pylori* infection has been studied in some of these populations and is known to be high.

The association between prior seropositivity for *H. pylori* and subsequent gastric cancer has been evaluated in three cohort studies, yielding 29–109 cases of gastric cancer. Significant positive associations were observed in all three, with estimated relative risks, based on case–control analyses within the cohorts, varying from 2.8 to 6.0. In a pooled analysis of the three studies, the relative risk was 3.8, which was significant, and there was a significant trend towards increasing estimated relative risks with increasing length of follow-up. In these cohort studies, potential confounding by dietary and other factors that have previously been associated with gastric cancer was not assessed. The extent to which such factors could have contributed to the association between gastric cancer and infection with *H. pylori* is difficult to estimate in view of the imprecision of assessments of past dietary habits.

Nine retrospective case–control studies have addressed the association between seroprevalence for *H. pylori* infection and incidence of gastric cancer. The estimated relative risks for gastric cancer were elevated in six studies, ranging from 1.2 to 4.2, and were significant in three studies. In a number of studies, the control series may not have been representative of the population that gave rise to the cases, either because of the method of sampling (e.g. subjects requiring gastrointestinal investigation) or because of exclusions on the basis of a history of gastric symptoms or disease.

When appropriate stratifications of the results of the prospective and retrospective studies were reported, the association between infection with *H. pylori* and gastric cancer was stronger in younger patients and for cancers at sites other than the cardia. The association was similarly strong for the intestinal and diffuse histological types of cancer.

The association between *H. pylori* infection and gastric lymphoma has been investigated in some studies. In two series of 110 and 178 patients with gastric B-cell mucosa-associated lymphoid tissue lymphomas, 92 and 98%, respectively, had histological evidence of *H. pylori* infection. In two studies of treatment, five of six patients and 12 of 16 patients showed tumour regression after therapy to eradicate *H. pylori*. Thirty-three cases of gastric non-Hodgkin's lymphoma were observed in a cohort study of patients with *H. pylori* infection in the USA and Norway, giving a significant estimated relative risk of 6.3.

5.3 Animal carcinogenicity data

No adequate study on *H. pylori* was available.

5.4 Other relevant data

The gastric precancerous process is characterized by sequential lesions of the gastric mucosa, namely chronic gastritis, atrophic gastritis, intestinal metaplasia and dysplasia. This constellation of lesions occurs in one major type of gastric adenocarcinoma, the intestinal type, the prevalence of which has been declining in developed countries. The other major type is diffuse carcinoma, which is becoming relatively more frequent in those countries and is associated with chronic nonatrophic gastritis.

H. pylori is the main cause of most types of chronic gastritis. This statement is supported by the observation that gastritis developed after voluntary ingestion of bacterial cultures, the consistent association between infection with the bacterium and gastritis throughout the world and the disappearance of gastritis after successful treatment of the infection.

Three independent cohort studies have shown the progression of gastritis from the non-atrophic to the atrophic form. Epidemiological studies of atrophic gastritis have also shown an association with dietary factors, especially excessive salt intake and inadequate consumption of fresh fruits and vegetables.

The bacteria are present in the human gastric stomach as extracellular colonies in the gastric mucus. In most patients, some bacteria adhere to the epithelial cells. Atrophic gastritis induced by *H. pylori* results in overgrowth of other bacteria.

Several *Helicobacter* species induce gastritis in many domestic and experimental animals. Infection with *H. felis* induced chronic gastritis followed by atrophy in mice.

The mechanisms by which *H. pylori* may increase the risk for gastric cancer are unknown. The bacterium has been shown to increase cell replication in the gastric mucosa. Some strains of *H. pylori* which induce inflammation of the gastric mucosa produce cytotoxin. Cytotoxin-associated strains are predominant in both gastric cancer patients and patients with both duodenal ulcer and atrophic gastritis. A protein associated with cytotoxin-positive *H. pylori* strains (cagA) induces expression of interleukin 8 in gastric mucosa, which appears to be correlated with degree of inflammation.

5.5 Evaluation[1]

There is *sufficient evidence* in humans for the carcinogenicity of infection with *Helicobacter pylori*.

There is *inadequate evidence* in experimental animals for the carcinogenicity of infection with *Helicobacter pylori*.

Overall evaluation[2]

Infection with *Helicobacter pylori* is carcinogenic to humans (Group 1).