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Schistosomes, Liver Flukes and *Helicobacter pylori*

Summary of Data Reported and Evaluation

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INFECTION WITH SCHISTOSOMES
(*Schistosoma haematobium*, *Schistosoma mansoni* and *Schistosoma japonicum*)
Schistosoma haematobium (Group 1)
Schistosoma mansoni (Group 3)
Schistosoma japonicum (Group 2B)

For definition of Groups, see Preamble Evaluation.

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5. Summary of Data Reported and Evaluation

5.1 Exposure data

Schistosomes are trematode worms that live in the bloodstream of human beings and animals. Three species (*Schistosoma haematobium*, *S. mansoni* and *S. japonicum*) account for the majority of human infections. People are infected by exposure to water containing the infective larvae (cercariae). The worms mature in the veins that drain the bladder (*S. haematobium*) or in the intestine (other species). The adults do not multiply in the body but live there for several years, producing eggs. Some eggs leave the body in the urine or faeces and hatch in water to liberate the miracidium larva, which infects certain types of freshwater snails. Within the snail, the parasites multiply asexually to produce free-swimming cercaria larvae, which infect people by skin penetration. Eggs remaining in the human body are trapped in the tissues, where they elicit hypersensitivity granulomas that cause disease in the urogenital system (*S. haematobium*) or in the liver and intestines (other species).

The diagnosis of infection with *Schistosoma* is based on simple qualitative and quantitative examinations of faeces and urine. *S. haematobium* infection is identified on the basis of a history of haematuria, observation of gross haematuria, detection of haematuria by chemical reagent strips or detection of eggs in urine by microscopy. *S. mansoni* and *S. japonicum* infections are identified by the presence of eggs in faeces. All infections can be quantified by egg counts in urine (*S. haematobium*) and faeces (other species). The available immunodiagnostic tests are useful for detecting light infections. Absence of infection can be established with certainty only by use of a combination of diagnostic tests.

Schistosomiasis occurs in at least 74 countries where 600 million people are at risk, of whom over 200 million are infected. The distribution of infection corresponds to the distribution of the snail hosts. Within endemic areas, transmission may be focal and can be localized to specific water sources. The intensity and frequency of exposure to contaminated freshwater determine the occurrence of the heavy infection that leads to disease. Prevalence and intensity of infection are usually correlated in endemic areas and especially in children. Sex differences in intensity of infection have been linked to differences in exposure. Death may be caused by urinary tract disease in *S. haematobium* infection and by portal hypertension in *S. mansoni* and *S. japonicum* infection.

Infection with *Schistosoma* is not synonymous with clinical disease, and many infections are asymptomatic. The outcome of infection is influenced by genetic factors, the immune response of the host and concomitant infections (e.g. hepatitis). Clinical disease is a sequel of heavy infection. Treatment of all forms of schistosomiasis with safe, effective antischistosomal drugs (i) results in a high rate of resolution of infection, (ii) prevents development of disease in people with heavy infection, (iii) arrests progression of existing severe disease and (iv) reverses some disease manifestations, particularly in children. Control of schistosomiasis has been achieved in some countries through combined approaches to intervention, including health education, improved water supplies and sanitation, environmental management, snail control and treatment.

5.2 Human carcinogenicity data

Schistosoma haematobium

A number of studies from Africa have shown that the estimated incidence of urinary bladder cancer is higher in areas with a high prevalence of infection with *S. haematobium* than in areas with a low prevalence. For example, urinary bladder cancer as a proportion of all cancer appears to be 10 times commoner among men in Egypt than among men in Algeria. Several other observations support an association between the occurrence of urinary bladder cancer and *S. haematobium* infection: the estimated incidence of urinary bladder cancer was related to the proportion of cancerous urinary bladder specimens containing *S. haematobium* eggs or egg remnants; the sex ratio of urinary bladder cancer cases varied widely and corresponded to the relative involvement of men and women in agricultural work (a risk factor for *S. haematobium* infection); and squamous-cell cancers of the urinary bladder were proportionately commoner in populations with a high prevalence of infection with S. hematobium and a high proportion of urinary bladder cancers showing histological evidence of infection than in areas without these characteristics.

Many cases of urinary bladder cancer have been reported in association with schistosomal infection of the urinary bladder. Other cancers have been reported in association with infection with *S. haematobium* including, particularly, cancer of the cervix.

Seven case-control studies of the association between *S. haematobium* infection and urinary bladder cancer have been reported. *S. haematobium* infection was measured variously by presence of eggs in urine, pelvic X-ray, rectal biopsy, biopsy of the urinary bladder and digestion and centrifugation of urinary bladder tissue. All of the studies were hospital-based and in none was the correspondence between the population giving rise to the cases and that sampled for the controls demonstrated or addressed in the analysis. Possible confounding by age and sex was not considered in four studies. In three of these four studies, the method of measurement of past infection with *S. haematobium* differed between cases and controls. Possible confounding by smoking was considered in only one study. Six of the seven studies showed significant, positive associations between the occurrence of urinary bladder cancer and infection with *S. haematobium*, with estimated relative risks ranging from 2 to 14. Confounding is not likely to explain the strong associations seen in these studies.

Schistosoma mansoni

A number of cases of liver cancer, colorectal cancer, giant follicular lymphoma and some other cancers have been reported in association with *S. mansoni* infection.

Schistosoma japonicum

Mortality from liver cancer and prevalence of infection with *S. japonicum* have been found to be positively correlated in Japan but not consistently so in China. Mortality from and, in one study, incidence of colorectal cancer were strongly, consistently and significantly correlated with various measures of infection with *S. japonicum* in many studies across provinces, counties and communes in China.

In three case-control studies of liver cancer and infection with *S. japonicum* in Japan and China, the estimated relative risks for the association varied from 2 to 10. The relative risk remained elevated in patients who did not have antigens to hepatitis virus. The two studies giving the highest estimated relative risks were hospital-based and did not address the issue of correspondence between the population giving rise to the cases and that sampled for the controls. In one of these studies, possible confounding by age and sex was not controlled for.

In one hospital-based case-control study of gastric cancer in Japan, the estimated relative risk for *S. japonicum* infection, based on the presence of eggs in tissue, was 1.8 and was significant. Possible confounding by age and sex was not controlled for, and the issue of correspondence between the population giving rise to the cases and that sampled for the controls was not addressed.

Three case-control studies of colorectal cancer and infection with *S. japonicum* have been reported from China and Japan. In one, the estimated relative risks for cancer of the colon in association with the presence of eggs

in tissue was about 2.5 and was significant. Possible confounding by age, sex, area of residence, smoking and family history of cancer of the colon was controlled for in this study. In the two other studies, the estimated relative risks were 1.2 for colon cancer in both studies and 8.3 for rectal cancer in one study with control for possible confounding by age, sex, place of residence and occupation.

5.3 Animal carcinogenicity data

Infection with *S. haematobium* has been studied in experiments in mice, rats, hamsters, opossums and nonhuman primates. In mice, hamsters and opossums, hyperplasia of the urinary bladder was observed; one tumour of the urinary bladder was reported in an opossum. The studies in rats were inadequate for evaluation. In nonhuman primates, hyperplasia of the urinary bladder and a few lesions described as tumours of the urinary bladder or ureter were reported. *S. haematobium* infection was also studied in animals treated with known urinary bladder carcinogens. Infection with the parasite increased urinary bladder tumour incidence in mice administered 2-acetylaminofluorene and in baboons treated with *N*-nitrosobutyl-4-hydroxybutylamine.

In one experiment with *Mastomys natalensis* infected with *S. mansoni*, an increased incidence of liver tumours was observed. One case report of a hepatocellular carcinoma in a chimpanzee with *S. mansoni* infection has been published. Infection with *S. mansoni* was studied in inadequate experiments in mice and hamsters. An increased incidence of liver tumours was seen in one experiment in mice infected with *S. mansoni* and treated with 2-amino-5-azotoluene and in one experiment in infected mice treated with 2-acetylamino-fluorene.

Infection of mice with *S. japonicum* resulted in a significantly increased incidence of liver tumours in one experiment. Infection with *S. japonicum* enhanced the liver tumour incidence in mice treated with 2-acetylaminofluorene in one experiment.

5.4 Other relevant data

S. haematobium induces chronic inflammation of the lower urinary tract, leading to obstruction, squamous metaplasia, urinary retention and secondary bacterial infections.

Carcinomas of the urinary bladder seen in association with *S. haematobium* infection are more frequently of the squamous-cell type than of the transitional-cell type. Some characteristics of *S. haematobium* infections of the urinary tract may be relevant to the genesis of squamous-cell carcinoma of the bladder. Inflammatory changes are seen in the mucosa of the lower urinary tract. Endogenous mutagenic and carcinogenic products are detected in increased concentrations in the urine of people infected with *S. haematobium*. Recurrent bacterial infection of the urinary tract, even in the absence of *S. haematobium* infection, is strongly associated with the appearance of squamous-cell carcinomas of the urinary bladder. In a small series of patients, mutations at the p53 gene in squamous-cell carcinomas found in association with *S. haematobium* infection were different from those in the transitional-cell malignancies of smokers.

S. mansoni and *S. japonicum* induce fibrosis of the liver and inflammatory lesions of the large bowel. There is some evidence that livers infected with *S. japonicum* (and other species) alter the metabolism of certain carcinogens.

5.5 Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of infection with *Schistosoma haematobium*.

There is *inadequate evidence* in humans for the carcinogenicity of infection with *Schistosoma mansoni*.

There is *limited evidence* in humans for the carcinogenicity of infection with *Schistosoma japonicum*.

There is *limited evidence* in experimental animals for the carcinogenicity of infection with *Schistosoma haematobium*.

There is *limited evidence* in experimental animals for the carcinogenicity of infection with Schisotosoma mansoni.

There is *limited evidence* in experimental animals for the carcinogenicity of infection with *Schistosoma japonicum*.

Overall evaluations

Infection with *Schistosoma haematobium* is *carcinogenic to humans (Group 1)*.

Infection with *Schistosoma mansoni* is *not classifiable as to its carcinogenicity to humans (Group 3)*.

Infection with *Schistosoma japonicum* is *possibly carcinogenic to humans (Group 2B)*.

For definition of the italicized terms, see Preamble Evaluation.

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INFECTION WITH LIVER FLUKES
(*Opisthorchis viverrini*, *Opisthorchis felineus* and *Clonorchis sinensis*)
Opisthorchis viverrini (Group 1)
Opisthorchis felineus (Group 3)
Clonorchis sinensis (Group 2A)

For definition of Groups, see Preamble Evaluation.

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5. Summary of Data Reported and Evaluation

5.1 Exposure data

The liver flukes, *Opisthorchis viverrini*, *O. felineus* and *Clonorchis sinensis*, are biologically similar, food-borne trematodes which chronically infect the bile ducts and, more rarely, the pancreatic duct and gall-bladder of human beings and other mammals. Infection is acquired by eating raw or undercooked freshwater fish which contain the infective stage (metacercaria) of flukes. Immature flukes migrate up through the ampulla of Vater to the biliary tree, mature in the small intrahepatic ducts and produce eggs, which are passed in the faeces. If the eggs reach a water body and are consumed by an appropriate species of snail, they hatch and undergo asexual multiplication to produce free-swimming larvae, which can penetrate freshwater fish and become encysted metacercariae.

Liver fluke infections are best detected by identification of eggs in the faeces. In light infections and severe disease with obstruction, eggs may not be found. There is a close quantitative relationship between the number of eggs per gram of faeces and the number of adult worms. Immunodiagnostic techniques cannot be used reliably to detect active infections.

Nine million people are infected with *O. viverrini*, which is common in North-east Thailand, at least one-third of the population being infected, and in North Thailand and Laos. *O. felineus* affects 1.5 million people, mainly in the central part of the Russian Federation. An estimated 7 million people are infected with *C. sinensis* in the Republic of Korea, southern China, Hong Kong, Macao and Viet Nam. The distribution of human infection is determined primarily by the distribution of the habit of eating raw freshwater fish; heterogeneity within endemic areas is probably due to environmental factors and control. Infection generally occurs during the first decade of life, often with a similar pattern in men and women, although men may be more frequently and heavily infected than women.

Most liver fluke infections lead to local inflammation, and they are associated with specific clinical signs and symptoms in 5-10% of infected people. The intensity of infection is correlated with hepatobiliary tract abnormalities visualized by ultrasound. Biliary and gall-bladder stones are commoner among individuals heavily infected with *Clonorchis* than among those infected with the other liver flukes. Treatment with praziquantel is highly effective and also leads to reversal of biliary tract abnormalities. Control of infection has been achieved in some areas by a combination of chemotherapy, health education and improved sanitation.

5.2 Human carcinogenicity data

Opisthorchis viverrini

Within Thailand, the highest proportional incidence rate of cholangiocarcinoma is observed in the north-east region of the country where the prevalence of infection with *O. viverrini* is also highest. In this region, the incidence of cholangiocarcinoma is about 40 times the highest incidence outside Thailand. A formal analysis across five regions of the country showed a strong correlation between proportional incidence of

cholangiocarcinoma and estimated average titres of antibodies to *O. viverrini* and, to a lesser degree, faecal egg count. Correlations with proportional incidence rates of hepatocellular carcinoma were much weaker.

Many cases of liver cancer arising in patients with *O. viverrini* infection have been reported from Thailand. In most regions of the world, cholangiocarcinoma is a very rare tumour. In areas where *O. viverrini* is endemic, however, the numbers of cases of cholangiocarcinoma generally outnumber those of hepatocellular carcinoma.

Three cross-sectional or case-control studies of the association between infection with *O. viverrini* and cancer of the liver have been reported from Thailand. In the earliest and smallest of these studies, the estimated relative risks for cholangiocarcinoma and hepatocellular carcinoma in association with the presence of *O. viverrini* eggs in faeces were each 1.3. In the second study, the estimated relative risk for the association between cholangiocarcinoma and the presence of *O. viverrini* antibodies in serum was 5.0, which was significant. The association was not explained by possible confounding with hepatitis B virus infection or estimated recent intake of aflatoxins. The estimated relative risk for the association with hepatocellular carcinoma was 1.7 (not significant). In the third study, based on 15 cases of cholangiocarcinoma, estimated relative risks of 1.7, 3.2 and 14.1 were calculated for categories of faecal excretion of increasing numbers of *O. viverrini* eggs. This trend was highly significant.

Opisthorchis felineus

The incidence of liver cancer was observed to be correlated with the prevalence of infection with *O. felineus* across four areas in the T'umen' region of north-west Siberia. Cases of both cholangiocarcinoma and hepatocellular carcinoma have been reported in people infected with *O. felineus*.

Clonorchis sinensis

Cases of cancer of the liver in association with infection with *C. sinensis* have been reported from China, Hong Kong, the Republic of Korea and Japan and in immigrants to North America from China and Laos.

Two case-control studies of the relationship between *C. sinensis* infection and liver cancer, with partially overlapping case series, have been carried out in the Republic of Korea. Significantly increased estimated relative risks of 6.5 and 6.0 were seen for an association with cholangiocarcinoma, but no significant association was seen with the occurrence of hepatocellular carcinoma. In a third case-control study, in Hong Kong, the estimated relative risk for cholangiocarcinoma, after adjustment for age and sex, was 3.1, while that for hepatocellular carcinoma was 0.7.

5.3 Animal carcinogenicity data

Infection with *O. viverrini* alone was evaluated in hamsters in several studies that were not designed specifically as long-term carcinogenicity studies. Two cholangiocarcinomas were found in one of these studies. In several studies in hamsters infected with *O. viverrini* and treated with various carcinogenic *N*-nitrosamines, induction of cholangiocarcinomas and of hepatocellular nodules was enhanced.

No study of the carcinogenicity of *O. felineus* was available.

Infection with *C. sinensis* was associated with the presence of a few cholangiocarcinomas in cats and one in a dog. Two experiments in rats were inadequate for evaluation. Infection with *C. sinensis* increased the incidence of cholangiocarcinomas in hamsters treated with 2-acetylaminofluorene or *N*-nitrosodimethylamine.

5.4 Other relevant data

The general pathological features of infection with liver flukes are similar in humans and animals. The changes

are characterized by oedema, desquamation and acute inflammatory cellular responses in the bile ducts in the early stage; in the chronic stage, the bile ducts show marked goblet-cell metaplasia, adenomatous hyperplasia and thickening of the walls. Complications may include calculi, suppurative cholangitis and biliary abscess caused by bile stagnation due to mechanical obstruction.

Cholangiocarcinomas appear to arise from pre-existing adenomatous changes in the bile ducts through the phase of intestinal metaplasia or dysplastic change.

The expression of CYP2A isozymes that catalyse the metabolism of aflatoxin and nitrosamines in the liver is increased in *O. viverrini*-infected hamsters. The increased expression is located in regions of the liver adjacent to the site of inflammation. The activity of macrophage-associated nitric oxide synthase is also increased in these animals. No information was available about the effects of liver fluke infection on carcinogen metabolism in humans. Increased urinary levels of nitrate and certain nitrosamines are detected in people infected with *O. viverrini*.

5.5 Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of infection with *Opisthorchis viverrini*.

There is *inadequate evidence* in humans for the carcinogenicity of infection with *Opisthorchis felineus*.

There is *limited evidence* in humans for the carcinogenicity of infection with *Clonorchis sinensis*.

There is *limited evidence* in experimental animals for the carcinogenicity of infection with *Opisthorchis viverrini*.

There is *inadequate evidence* in experimental animals for the carcinogenicity of infection with *Opisthorchis felineus*.

There is *limited evidence* in experimental animals for the carcinogenicity of infection with *Clonorchis sinensis*.

In making the overall evaluation, the Working Group noted that experimental and epidemiological studies on *Clonorchis sinensis* confirm:

(i) that the biological and pathological characteristics of *Opisthorchis* and *Clonorchis* are similar;

(ii) that cholangiocarcinoma occurs in infected animals, especially when infection is combined with administration of known carcinogens; and

(iii) that the relative risks for cholangiocarcinoma, and not for hepatocellular carcinoma, are consistently increased in people infected with this organism.

Overall evaluations

Infection with *Opisthorchis viverrini* is *carcinogenic to humans (Group 1)*.

Infection with *Opisthorchis felineus* is *not classifiable as to its carcinogenicity to humans (Group 3)*.

Infection with *Clonorchis sinensis* is *probably carcinogenic to humans (Group 2A)*.

For definition of the italicized terms, see Preamble Evaluation.

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INFECTION WITH *HELICOBACTER PYLORI* (Group 1)

For definition of Groups, see Preamble Evaluation.

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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 sero-prevalence 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

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

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

For definition of the italicized terms, see Preamble Evaluation.

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