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 anti-schistosomal 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-acetylaminofluorene.

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).