WHO/CDS/CPE/PVC/2002.4

Report of the WHO Informal Consultation on the use of Praziquantel during Pregnancy/Lactation and Albendazole/Mebendazole in Children under 24 months

Geneva
8-9 April 2002

World Health Organization
Strategy Development and Monitoring
for Parasitic Diseases and Vector Control (PVC)
Prevention, Control and Eradication (CPE)
Communicable Diseases (CDS)
http://www.who.int/ctd

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1. Purpose of the consultation

During the WHO Joint Expert Committee meeting on the Prevention and Control of Schistosomiasis and Soil-transmitted Helminthiasis (8-14 October 2001), the participating experts felt that the current WHO recommendations to avoid using praziquantel during pregnancy and lactation and mebendazole or albendazole in children under two years of age, needed to be reviewed and possibly revised.

The Committee recognized that pregnant women suffering from schistosomiasis are currently left untreated often for 9 months to a year and that this disease has serious adverse effects on them and their pregnancy outcomes. In addition, the WHO recommendation not to treat lactating women for schistosomiasis can result in treatment delays of years in countries where women are pregnant or lactating for a substantial part of their reproductive life. Current practice in Egypt, China and the Philippines is to treat lactating women and have them stop breast-feeding for 24-48 hours. It is unlikely, however, that the small amount of praziquantel present in breast milk induces any toxicity in infants. The results of a risk-benefit analysis presented during the Expert Committee meeting indicated that treatment with praziquantel should be recommended.

There is growing evidence to suggest that soil-transmitted helminthiasis has a detrimental effect on the growth and development of children under 24 months of age. Although there is little published information about the use of anthelminthic drugs in this age group, such data as exist offer no obvious reason for excluding children of this age group from treatment. In view of the need to strengthen health care for children in this section of the community, the Expert Committee also urged WHO to assess the aspects and consequences of treating children under 24 months of age with benzimidazoles against soil-transmitted helminthiasis.

Accordingly, on the basis of the published results of animal studies, veterinary usage and wide experience of using anthelminthic drugs in humans under clinical conditions, the Committee proposed that WHO should hold an Informal Consultation as a matter of urgency to assess all aspects of the use of praziquantel during pregnancy and lactation, as well as those issues related to the use of benzimidazoles in children under 24 months of age.

2. Public health significance of schistosomiasis in pregnant and lactating women

It was recently estimated that the global number of cases of infection with *Schistosoma* spp is still around 200 million, with 650 million being at risk of infection (Chitsulo et al., 2000). This water-borne infection is endemic in the Caribbean, S. America, Asia and Africa. In sub-Saharan Africa alone there are reckoned to be 112 million infections with *Schistosoma haematobium* and 54 million with *S. mansoni* (Van der Werf et al., 2003). Transmission intensities vary and are highly focal depending on human contact with contaminated water. Progress has been made in controlling infections and reducing transmission in several countries including Brazil, China, Egypt and the Philippines. It is estimated that today there are less than 2 million people infected with *S. japonicum* or *S. mekongi* (Jiang et al., 2002; Urbani et al., 2002).

Recent accurate data on the number of pregnant and lactating women occurring at any given time are difficult to obtain. Rough estimates suggest that 124 million women worldwide are likely to be pregnant. Reliable predictions for the concurrence of pregnancy and schistosomiasis and lactation and schistosomiasis have yet to be made. However, rough estimates indicate that 10 million women annually could have schistosomiasis during pregnancy today in Africa alone. The situation may reveal a similar pattern to that found for the relationship between hookworm infections and pregnancy (WHO, 1996a). For

example, in 1990 some 24 million women were reckoned to be pregnant in sub-Saharan Africa and up to 7.8 million of these were probably infected with hookworms. Depleted iron status and iron deficiency anaemia (IDA) are commonly found to affect adversely the course of pregnancy and birth outcome (Stephenson, Latham & Ottesen, 2000a). Hookworms impair iron status and induce IDA. Schistosome infections causes chronic blood loss, consume erythrocytes and so impair iron status in addition to causing serious end organ damage (section 5).

Women aged 18-45 years and living where schistosomiasis is endemic may spend up to 25% of their reproductive life pregnant and 60% of the time lactating. The availability of good quality, cheap praziquantel provides the best means of bringing relief from the debilitating effects of schistosomiasis to this segment of the population. Furthermore the effects of schistosomiasis in adolescent girls should not be overlooked.

3. Public health significance of soil-transmitted helminthiasis in children under 24 months

Children aged 24 months and less make up between 5 and 10% of the 3.5 billion people either infected with or at risk of infection from *Ascaris lumbricoides* (roundworm), *Ancylostoma duodenale* and *Necator americanus* (hookworms) and *Trichuris trichiura* (whipworm). Results from epidemiological studies of babies and infants in this age group have rarely been published and such data as are available suggest that these infections do not become established until at least 6 months of age or when weaning begins. Results from 12 surveys of children less than 24 months of age collected by Montresor, Awasthi & Crompton (2003) showed prevalences of STH to range from 20 to 80%. The data in these publications indicated that infections are usually acquired by children older than 12 months. Similar observations have been made in other publications which focused on the 0 to 4 year-old age class. The possibility of these

infections occurring in children aged 24 months and less should not be ignored. Furthermore, soil-transmitted helminthiasis has undoubted public health significance for pre-school and older children (Stephenson, Holland & Ottesen, 2000b; Stoltzfus et al., 2001).

4. Pathophysiological aspects

4.1 Schistosomiasis during pregnancy and lactation

Schistosomiasis is complicated by specific end organ pathology including hepatic fibrosis and malfunction, urinary obstruction, bladder cancer and other lesions (Ross et al., 2002). The basis for this pathology is found in the host's immune response to eggs trapped in the tissues. End organ morbidity was thought to develop slowly, but more recent research suggests that this process occurs faster in regions of high infection intensity and in relation to an individual's genetic make up (Ross et al., 2002).

Pregnant and lactating women are as susceptible to end organ damage as anyone else. The fact that the lesions may develop more rapidly than was previously thought means that delays in treatment of an infected woman until she is no longer pregnant or lactating are likely to result in major end organ morbidity. Although morbidity declines following treatment with PZQ, bladder lesions and hepatic fibrosis do not completely resolve.

'Subtle' morbidity including anaemia, growth stunting, decreased work capacity and reduced cognition is associated with schistosomiasis (Brabin et al., 1998; Hassan, el-Hussinie & el-Nahal, 1999; Nokes et al., 1999). In a double-blind placebo-controlled trial, the overall blood haemoglobin concentration in a study population rose by 0.3g/l over 6 months following treatment with PZQ (Olds et al., 1996). This statistically significant improvement, without iron supplementation, indicates that iron status also improved with treatment. Another blinded placebo-controlled trial led to a similar conclusion (McGarvey et al., 1996).

The impact of schistosomiasis on child growth and development is greatest during the adolescent growth spurt and has been most clearly demonstrated for *Schistosoma japonicum* (Olds et al., 1996). Treatment with PZQ to cure schistosomiasis enhanced growth and halted the declining growth rate. It is not known if maternal schistosomiasis affects the growth of the fetus *in utero.*

Small quantities of PZQ can be detected in mammalian milk following treatment. Its concentration in breast milk is estimated to be 25-30% of the mother's serum concentration. A suckling infant would ingest in a feed at maximum 0.1% of the weight-adjusted maternal dose (Putter & Held, 1979). Nonetheless, breastfeeding is currently withheld for 24-48h if the mother is to be treated with PZQ. This practice has continued despite the knowledge that PZQ is routinely used in farm and companion animals during lactation without any noticeable effects of the very low amount of PZQ passed. A recent review of this issue (Olds, 2003), including a cost-benefit analysis, advocates praziquantel treatment of pregnant and lactating women with schistosomiasis.

4.2 Soil-transmitted helminthiasis during early childhood (0-24 months)

Few published results are available concerning the adverse effects of soil-transmitted nematode infections on infants particularly when compared with results involving school-age children. This situation creates difficulties for Human Subject Review Committees for two reasons. First, most study designs depend on intervention with an anthelminthic drug and, secondly, there remains a paucity of data about the prevalence and intensity of these infections in very young children. An analysis of the current position is to be found in a recent review by Montresor, Awasthi & Crompton (2003).

Ten studies concerned with the effect of soil-transmitted helminthiasis on the health of children in this age group have shown that deworming is accompanied by the following benefits:

- improved helminth status (decreases in prevalence and intensity);
- improved nutritional status (increased weight gain); and
- improved iron status in anaemic children (Montresor, Awasthi & Crompton, 2003).

Deworming was carried out with albendazole in 8 studies and with mebendazole in two. There was no evidence of adverse effects with either benzimidazole, indicating that these drugs can be used to treat young children safely and effectively.

5. **Praziquantel (PZQ)**

5.1 Mode of action

The precise mode of action of Praziquantel is not known but it rapidly causes tegumental damage and paralytic muscular contraction of parasites, followed by their death and elimination, possibly due to an action on parasite glutathione S-transferase (GST) and the intracellular calcium level, with secondary effects on metabolism and exposure or release of concealed antigens (Dollery, 1999a).

5.2 Pharmacokinetics

Absorption is 75-100% of an oral dose in rat, dog, monkey and humans; the maximum is reached after 30-120 minutes in animals and 3-4 hours in humans. A carbohydrate-rich meal enhances absorption in humans (Mandour et al., 1990). Co-administration of chloroquine and pre-administration of carbamazepine and phenytoin may reduce bioavailability of PZQ (Bittencourt, Garcia & Martins, 1992; Masimirembwa & Hasler, 1994). In humans, metabolites are completely cleared

within four days after an oral dose, but in most other species clearance of the parent drug takes 1-2 hours and of metabolites 3-8 hours (Dollery, 1999a). Excretion is predominantly as metabolites and some parent drug in urine. In humans about 80% of a dose is excreted in the urine. PZQ and its principal metabolites are found in human milk at levels about 25-30% of those in maternal plasma.

5.3 Toxicity

At the time of the original development of PZQ extensive accounts of the principal toxicological findings were published (Frohberg, 1984). The most significant for acute toxicity are as follows:

Oral LD50 mouse 2454 mg/kg, rat 2840mg/kg and rabbit about 1050/kg (Frohberg, 1984). In repeated dose toxicity studies no drug-related lesions were noted in rats treated with PZQ up to 1000mg/kg/d for four weeks and in beagle dogs up to 180mg/kg/d for 13 weeks.

Genetic toxicity. PZQ lacks mutagenic potential in humans (Frohberg, 1984; EMEA, 1996).

Reproductive toxicity. PZQ has no harmful effects on fertility, fetal and maternal toxicity in animal reproductive toxicity and teratogenicity studies using up to 300mg/kg/d in the rat and rabbit, and in embryotoxicity studies in the mouse, rat and rabbit. PZQ is widely approved for medicinal use in cats, dogs and sheep including pregnant animals.

Carcinogenicity. The drug was not found to be carcinogenic in rats or hamsters treated for 104 and 80 weeks, respectively (Frohberg, 1984). In summary, reviews of original reports and their evaluation by official agencies have concluded that PZQ lacks significant toxic potential in laboratory experiments.

5.4 Notified inadvertent use and recorded adverse effects

Currently, the manufacturers do not recommend the use of PZQ during the first three months of pregnancy although animal studies provide no evidence to indicate that the mother and unborn offspring will be adversely affected. A total of 6 cases of inadvertent use during pregnancy have been reported to Bayer. One further case was reported to Merck. All the reports emanated from countries where schistosomiasis is non-endemic: 3 from the UK, 1 from France, 1 from Switzerland, 1 from Germany and 1 from the US. No formal reports have been made from the countries where human schistosomiasis is endemic. Of the 6 cases reported to Bayer, 1 was excluded as treatment had occurred before the pregnancy. Of the remaining cases, 3 of them involved a pregnant patient infected with schistosomiasis, 2 had neurocysticercosis and 1 an unspecified cestode infection. Birth of a normal baby was reported in 4 cases; 2 cases were lost to follow-up. One baby was reported to have anaemia, but it was concluded that insufficient information was provided for a causality assessment.

No estimate could be provided for the total number of doses delivered in endemic countries in order to put the seven reported cases in a population-based context.

6. **Albendazole (ALB)**

6.1 Mode of action

Albendazole binds to intracellular tubulin, selectively affecting helminths and inhibiting essential absorptive functions in the organism.

6.2 Pharmacokinetics

In the mouse and rat, oral absorption of albendazole is 20-30% and in cattle about 50%, compared with 1-5% in humans

(Dollery, 1999b; EMEA, 1997; JECFA, 1989a; JECFA,1989b). Absorption in animals and humans is rapid, within 2-3 hours in humans, rats and sheep. Food enhances absorption up to 5-fold in humans and animals. Fasting increases absorption in calves. Clearance of the parent drug is rapid in all species but that of the metabolites, albendazole sulphoxide and sulphone, is slower. Formation and elimination of ALB sulphoxide is important because it is believed to be the main active form of the drug. The half-life time of ALB sulphoxide is 8-12 hours in humans. The metabolism and clearance of ALB follow similar pathways in humans and other species (Dollery, 1999b; EMEA, 1997), except that the rate of formation of the positive enantiomer, which appears to be more biologically active than the negative form, is more rapid in humans and domestic animals than in laboratory animals (Dollery, 1999b). The comprehensive safety data in many food animals, and in the rat and rabbit, are reassuring.

Data are lacking on the excretion of albendazole in human milk, but it is known to occur in multigastric animals (cows and sheep) where the half-life of the metabolites is considerably longer (>48 hours).

6.3 Toxicity

The oral LD50 for the mouse is >3000mg/kg, for the rat is 1320-2400mg/kg and for the rabbit 500-1250mg/kg. Repeated administration of ALB in doses larger than 30-40mg/kg/d for 90 days caused retardation of weight gain and reversible anaemia.

Genetic toxicity. ALB**,** like other benzimidazoles, is genotoxic in *in vitro* cytogenetic testing, such as the mouse bone marrow micronucleus test. Albendazole probably acts as an aneuploidogen. Aneuploidogens are considered to have a threshold exposure below the threshold that will not represent a risk to humans or animals (Committee on Mutagenicity, 1996; Aardema et al., 1998).

Carcinogenicity testing. There is no evidence of carcinogenicity in the rat or mouse over 24 months using doses of 400mg/kg/d.

Reproductive toxicity testing. Extensive studies of laboratory and farm animals have shown that high doses of ALB may cause embryonic death and other damage, but always after considerably higher exposures than those ever produced in clinical practice (JECFA, 1989 a; JECFA 1989b; PDR 2001).

6.4 Notified inadvertent use and recorded adverse effects

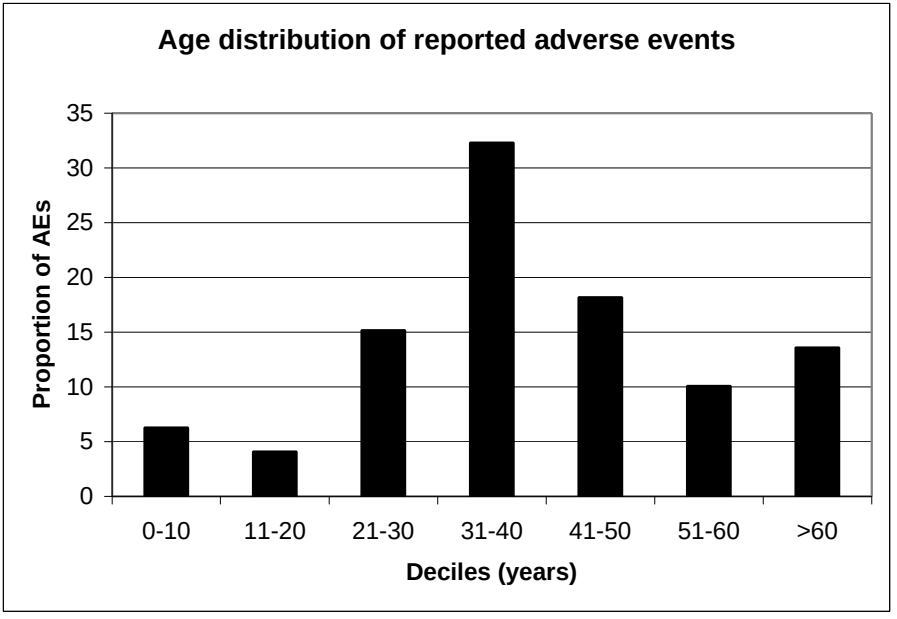
Since albendazole was first introduced for human use in 1982, the nature of exposure has changed, and this has bearing on the adverse event profile of the compound. It is estimated that one billion patients have received GlaxoSmithKline (GSK) manufactured albendazole and a further 200 million have received generic products. The data provided to the Informal Consultation were drawn from two sources:

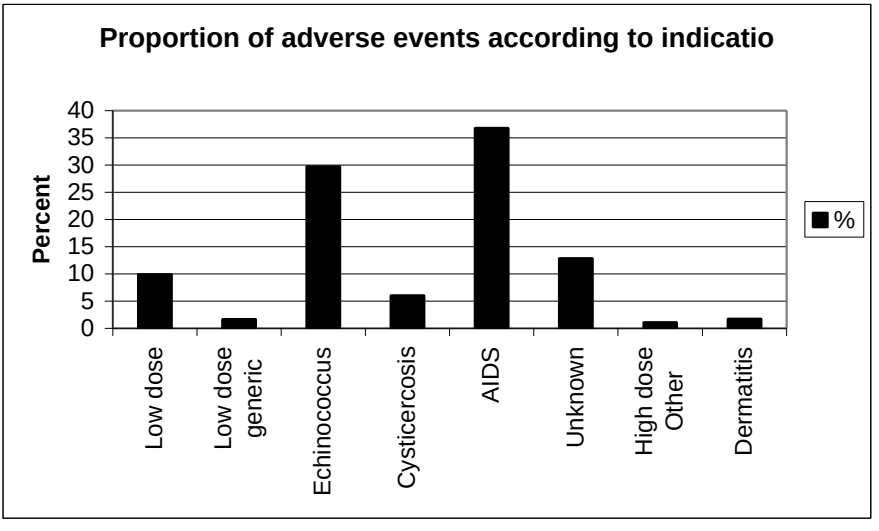
(i) adverse event reporting procedures to GSK- the reports from a Product Safety Update Review (PSUR); and
(ii) published data from clinical trials.

Some 732 patients with adverse events to albendazole are recorded in the GSK safety database. The vast majority were in adults and are attributed to high-dose treatment for echinococcosis (400mg twice daily for 3 months or more) or for opportunistic infections in AIDS patients (where doses of 400-800mg twice daily have been used continually for weeks or months in the management of microsporidial diarrhoea). Low-dose indications (400mg single dose daily for 5 days) account for 10% of all events. Of the 732 individuals in the database, 7 (1%) were aged 2 years or less. Significant clinical events are rare in these young children and the adverse events recorded include local hypersensitivity and worm migration.

A further source of information, published data from clinical trials using low-dose albendazole (similar to that used for

intestinal helminth infections) was also provided. Information was available for 22,000 patients out of a potential 35,000 who had been treated. A low frequency of GI (abdominal pain and diarrhoea) and CNS (headache) symptoms predominate, but the incidence of any event occurring with low dose treatment is extremely low (see graphs overleaf).





Age distribution and distribution according to indications or dose level of reported adverse events following the use of albendazole [courtesy of GlaxoSmithKline]

7. **Mebendazole (MBD)**

7.1 Mode of action

Mebendazole is believed to act by binding to and inhibiting essential intracellular microtubule-dependent transport processes in the parasite (Dollery, 1999c; EMEA, 1999; EMEA, 2001).

7.2 Pharmacokinetics

Oral absorption in all species is limited; from 17-22% in healthy adult human volunteers (Dollery, 1999c). The plasma concentration of mebendazole is 15-49 times lower than that of albendazole. Clearance, which is dependent upon metabolism in the liver, occurs predominantly as metabolites in bile and urine and there is much unchanged drug in the faeces. Co-administration with a fatty meal enhances absorption. Excretion in breast milk has not been reported.

7.3 Toxicity

The oral LD50 in the rat is 1434mg/kg in males and 714mg/kg in females and for other species, such as the rabbit, is >1280mg/kg. In repeated dose testing, rats receiving doses up to 127.3 (males) - 151.6 (females) mg/kg/d for 13 weeks demonstrated growth retardation, anaemia and some deaths. Testicular damage was also observed in male rats receiving the highest doses.

Genetic toxicity. MBD, like ALB, is a clastogen and aneugen *in vitro*. This is considered to occur only with a threshold dose and not to represent a risk to humans receiving conventional therapy. The published reports are inadequate concerning carcinogenicity testing. Agencies assessing the use of MBD in animal feed have not raised major concerns about the data submitted to them.

Reproduction toxicity. MBD is a teratogen in the rat at certain doses but not in the rabbit (Dollery, 1999c; EMEA, 1999).
In the rat, the NOEL for fetotoxicity and teratogenicity is 10mg/kg/d; skeletal and limb abnormalities were produced.

Rabbits have been given up to 40mg/kg/d during gestation without fetal damage. MBD is not teratogenic in pigs, dogs, cats, sheep and horses (EMEA, 1999; EMEA, 2001).

Although MBD in high doses causes fetal toxicity and teratogenicity in the rat, but not in other species, there has been a clear demonstration of a NOEL in the rat, at 10mg/kg/d during gestation.

The 'Datasheet' for the use of MBD in humans in Britain and the USA notes that it is contraindicated in pregnancy (ABPI, 1999; PDR, 2001). From the veterinary viewpoint, EMEA (1999; EMEA, 2001) has maintained a ban on its use in animals from which milk for human consumption food will be obtained (except after a 14-day withholding period), whilst permitting its use in pregnant sheep and cattle.

Carcinogenicity testing. The only published information shows that technically inadequate carcinogenicity tests in the rat and mouse did not reveal oncogenic action in animals given up to 40mg/kg/d for 23-24 months (EMEA, 2001).

7.4 Notified inadvertent use and recorded adverse effects

A total of 614 spontaneous reports on adverse events disregarding a cause relationship have been reported to Janssen. Of these, 310 were associated with the 100mg tablet, 14 with the 500mg tablet as a single dose and 8 with the 500mg tablet taken for several days. Of the remaining 282, the formulation was not stated. The majority of reported adverse events can be classified in two groups: transient abdominal pain and diarrhoea, and - in the case of heavy worm burden - hypersensitivity reactions such as eczema, rash, urticaria and angio-oedema. Adverse effects are rare considering that during the period 1981-1998 there have been 389 million patient exposures for the 100mg tablets; 192 million for the 200mg tablets, and 117 million for the 500 mg tablets.

8. Conclusions concerning the use of praziquantel (PQZ) for the treatment of schistosomiasis during pregnancy and lactation

- PZQ has high selective toxicity for adult schistosomes.

- The drug's PK and PD have not been found to show any material differences or changes when used during pregnancy.

- Toxicity and teratogenicity testing and studies of laboratory, companion and farm animals have not detected any harmful effects of PZQ on fertility or on maternal and fetal health.

- PZQ is extensively used by veterinarians to treat pregnant mammals with no known adverse effects on mothers and offspring.

- Recent human safety data, which does not include pregnancy, refer to abdominal cramps, diarrhoea, headache, nausea and a systemic reaction to dying schistosomes when treatment is given with PZQ.

- Data maintained at the WHO International Monitoring Centre for Adverse Drug Event Monitoring at Uppsala, Sweden, have provided no records of treatment of schistosomiasis with PZQ being linked to reproductive toxicity.

- In the absence of any evidence of human reproductive or fetal toxicity in normal therapeutic doses, there are no reasons to expect that the safety of PZQ is different in the pregnant and non-pregnant woman.

- PZQ has been proscribed for use in pregnancy and contraindicated because no controlled trials have been conducted to investigate the use of PZQ in pregnancy and lactation.

- The use of PZQ by veterinarians in lactating mammals has not led to detectable adverse effects in suckling offspring.

- Treatment of a mother during lactation with a recommended single dose of PZQ would result in her infant ingesting a maximum of 0.1% of the weight-adjusted maternal dose.

- PZQ may be regarded as safe for the treatment of schistosomiasis during lactation.

9. Conclusions concerning the use of albendazole (ALB) and mebendazole (MBD) in the treatment of soil-transmitted helminthiasis in children under 24 months

- Unmetabolized ALB is directly effective against intestinal nematodes in the alimentary tract.

- Enzymes responsible for the metabolism and catabolism of ALB and MBD (both benzimidazoles) attain adult levels of activity in children aged from 10 to 24 months of age.

- In infants and children aged 8 months and older, benzimidazole toxicity is not enhanced by the developmental stage of the factors involved in drug absorption.

- The risk of benzimidazole toxicity in children older than 12 months is not increased by the stage of development of the determinants of drug distribution

- Benzimidazole metabolism depends on oxidation by hepatic cytochrome P450. After birth, the cytochrome system matures rapidly, but the rate at which different enzymes reach adult levels varies considerably. Although children metabolize drugs at different rates from adults, with the benzimidazoles this seems not to be a problem from the toxicological point of view, since the drugs are well tolerated at high and prolonged dosages.

- Albendazole sulphoxide is the main systemic metabolite of ALB and it is responsible for the activity of the drug against systemic parasites (such as *Echinococcus*), but not intestinal helminths. It is not known how the body composition and function of young infants respond to the metabolites of ALB.

- There is extensive veterinary experience of MBD demonstrating <1-2% absorption from the gastrointestinal tract, < 2% bioavailability and about 90% elimination in the faeces.

- From veterinary experience, there is no evidence of MBD having any reproductive toxicity when used as recommended.

- Recent work in Tanzania administered 317 doses of MBD (500mg tablet) to 212 children under 24 months (of which 114 were between 6 and 12 months of age at the beginning of the study). The drug was found to be well tolerated without any reports of adverse side effects

- There is a paucity of safety data regarding the use of benzimidazoles in infants under 12 months.

- Formal, regulatory agency-approved advice excludes the use of ALB and MBD in children under 12 months.

10. **Drug interactions**

The possibility that a drug or its metabolites might interact with another drug or its metabolites cannot be ignored. A recent study involving albendazole and ivermectin, carried out in preparation for the programme for the global elimination of lymphatic filariasis, did not detect any adverse effects when given to patients concurrently (Horton et al., 2000). The possibility of a drug's pharmacokinetics or safety profile changing if given to a helminth-infected HIV positive or AIDS patient should also be considered.

There is some evidence to suggest that the course of HIV infection might be accelerated by schistosomiasis. Genital lesions, characteristic of infection with *Schistosoma haematobium*, are thought to facilitate transmission of sexually-transmitted diseases including HIV (Poggensee & Feldmeier, 2001; Feldmeier, Kranz & Poggensee, 1995). Treatment with PZQ in such cases is likely to be of public health benefit.

11. Benefits of schistosomiasis treatment for the health of pregnant and lactating women and for birth outcome

Much accumulated clinical experience has shown that anthelminthic treatment, with praziquantel, for both urinary and intestinal schistosomiasis leads to better health. Lesions typical of end organ morbidity are reversed or reduced. Adverse effects of more subtle morbidity, such as anaemia and poor iron status are relieved. These benefits have been recorded in children, men and women who were neither pregnant nor lactating at the time of treatment. There is no reason to expect that the same benefits would not be found in pregnant and lactating women with schistosomiasis if treated with praziquantel, given the excellent safety record of the drug during 20 years of use around the world.

Other benefits may be expected to accrue from treatment of pregnant and lactating women for schistosomiasis. Recovery from poor iron status and iron deficiency anaemia, particularly that associated with *Schistosoma haematobium* infection, will benefit the health and productivity of a woman both during pregnancy and lactation and will ease the burden on her caring for her other children and maintaining her domestic routine. Relief from anaemia improves the transfer of iron to the fetus and the suckling infant. Poor iron status during pregnancy is a major determinant of low birth weight which contributes significantly to the high infant mortality rates observed in countries where schistosomiasis is endemic.

12. Benefits of soil-transmitted helminthiasis treatment for the health of children under 24 months

Data from studies in Africa, Asia and Latin America, that included children below the age of two years, was provided to the Informal Consultation. Albendazole was the drug chosen for treatment in eight studies and mebendazole in two. In a recent study in Tanzania with children aged 6 to 59 months (212 were less than 24 months), mebendazole was the drug of treatment and parasitological, nutritional and cognitive variables were assessed. Mebendazole had a positive effect on motor and language development (comparison between the mebendazole-treated and placebo-treated children revealed no differences in the occurrence of adverse effects (fever, cough, diarrhoea, dysentery and acute respiratory illness) one week after intervention. The benefits of quarterly treatment with MBD and iron supplementation reported in these young children included the following:

- reduction in parasite prevalence and/or intensity after treatment;
- reduction in wasting malnutrition over an 18-month period in mebendazole-treated children recruited at 0.5 to 1 year (Stoltzfus et al., 2003);
- reduction in the risk of stunting in treated children compared with placebo monitored over two years (Stoltzfus et al., 2003);
- lack of adverse reactions in children under 24 months after treatment with mebendazole (Montresor et al., 2002); and
- evidence that supplementation with vitamin A and iron can be provided safely with anthelminthic treatment.

Most of the studies that have been done involved small sample sizes and in some cases parasitological data, including measures of intensity of infection, were lacking.

13. Risk analysis of using praziquantel to treat pregnant and lactating women for schistosomiasis

Thorough reviews of information about the non-clinical toxicity of PZQ, a detailed critique of the drug's pharmacodynamics, pharmacokinetics and use in laboratory, companion and farm animals and in humans convinced the Informal Consultation of the opinion that PZQ is safe to use during pregnancy and lactation. Any risk to the health of a woman, to her unborn child or suckling infant if it exists, is very small.

That schistosomiasis, through its end organ pathology and morbidity such as anaemia, is a severely debilitating disease can no longer be questioned. Health authorities appear to have over interpreted the cautious prescribing instruction from the Research-based Pharmaceutical Industry and WHO (Appendix II). The outcome of this over-interpretation, is that many women are excluded from treatment campaigns with PZQ, often for years. It is important to note that statements such as "it is preferable to delay treatment until after delivery" do not specifically exclude pregnant women from treatment for schistosomiasis and certainly have no bearing on lactation.

Adolescent girls suffering from schistosomiasis are equally in need of treatment with PZQ to enhance preparation for motherhood. All girls and women of childbearing age should be brought into PZQ treatment programmes.

The benefits of using PZQ to treat schistosomiasis in school-age girls, adolescent girls, women of reproductive age and pregnant and lactating women overwhelmingly outweigh any potential risks of adverse effects of the drug. In pregnancy, there is no reason to exclude patients from treatment during the first trimester and, in areas of high endemicity, no requirement for diagnosis. In areas of lower endemicity, screening is appropriate and those judged to be infected should be treated as a high-risk group.

14. Risk analysis of using albendazole or mebendazole to treat children under 24 months for soil-transmitted helminthiasis

There is a comprehensive literature compiled from research over 20 years to show that infections with soil-transmitted helminths cause significant morbidity in children between the ages of 2 and 14. It is reasonable to expect that impaired growth and development would be caused by these infections in younger children. There is, however, limited evidence to support this expectation. Such studies that have been done indicate that children under 24 months are likely to benefit if soil-transmitted helminthiasis is treated with the appropriate dose of either ALB or MBD, or other WHO-recommended drugs (Appendix II).

Regarding the use of ALB or MBD, which have been thoroughly safety tested and widely given to children, the main difficulty concerns the dose appropriate for the younger children (12 months and less). Apart from the likelihood of both prevalence and intensity being relatively low in infants from areas where soil-transmitted helminthiasis is endemic, there are questions of efficacy and safety when using an anthelminthic drug in very young children.

For example, is a 500mg tablet of MEB needed to treat a child younger than 12 months, assuming that treatment is warranted? Would a 250mg tablet be equally efficacious? There are several reasons to question safety. First, physical growth, maturation, acquisition of immune competence and psychological development occur rapidly during the first year, but these changes take place in discontinuous bursts rather than smoothly. Total body water (TBW), as a percentage of body weight, changes during the first year from 78% to 60%, the latter reflecting more closely the adult composition. Knowledge of TBW is essential for understanding a drug's distribution in the body and calculating the correct dosage. Furthermore, TBW affects the concentration of plasma proteins to which drugs bind. Renal function and the baby's capacity to metabolize and detoxify drugs at birth are factors that can also influence pharmacodynamics. The Informal

Consultation concluded that current knowledge is too sparse to recommend the use of ALB and MEB in children under 12 months of age.

The Informal Consultation recommended that infants (younger than 12 months) suffering from soil-transmitted helminthiasis should be referred to a physician for treatment on a case-by-case basis.

15. Use of levamisole (LEV) and pyrantel (PYR) in children under 24 months for the treatment of soil-transmitted helminthiasis

These widely-used, WHO-recommended anthelminthic drugs for the treatment of soil-transmitted helminthiasis (WHO, 1996b; WHO, 1999), were not discussed because their original manufacturers in the Research-based Pharmaceutical Industry did not exclude their use in children under 24 months. The Informal Consultation recognizes that health authorities in the endemic countries must select the most appropriate drugs to be used in programmes to control morbidity due to soil-transmitted helminthiasis. LEV and PYR remain available for use according to WHO recommendations (WHO, 2000; WHO, 2002a).

16. Drug procurement, quality assurance and monitoring

When planning and implementing measures to reduce morbidity due to helminth infections, the most appropriate means of ensuring a sustainable supply and distribution of drugs is to rely on a well functioning national drug procurement, distribution and delivery system. If national systems for drug procurement are not in place, WHO has the mandate to assist Member States with drug procurement (resolution WHA 28.66: see WHO, 2002b).

Independent analyses of generic versions of WHO-recommended drugs have found them to be of good quality. Nevertheless, sub-standard products are known to be on the market and programme

managers are advised not to purchase drugs without assurance of quality. Technical advice is available from WHO.

Mechanisms should be introduced and maintained for (a) monitoring control programmes and (b) reporting side effects and adverse reactions following chemotherapy (pharmacovigilance). The Informal Consultation is particularly concerned that reporting on the outcomes of using PZQ, ALB and MBD in the target groups under discussion should not be overlooked.

17. Issues requiring further attention

1) Interactions with HIV infections:
   a) pharmacovigilance designed in a way to take into account HIV and AIDS; and
   b) explore the possible protective effects of PZQ treatment in pregnant women against the progression of HIV infection.

2) Pharmacovigilance of PZQ in pregnancy and benzimidazoles in children less than 12 months.

3) Quality assessment of generic drugs to ensure safety and efficacy.

4) Strategies on how to reach children under 24 months and how to deliver treatment (selective, targeted, universal).

5) Mechanism of benzimidazole treatment benefits in children less than 2 years of age with light infections.

6) Separate the effects of each species of helminths: identify which will be the prime species responsible for pathologies in young children.

7) Documentation of presence of PZQ in breast milk in treated women and its effect on the newborn.

8) There is emerging evidence of benefits of anthelminthics treatment in children under 24 months. Further evidence is urgently needed to elucidate the impact of soil-transmitted helminthiasis on this vulnerable age group.

9) More research should be undertaken to establish the optimal dosages of anthelminthics in order to maximize the efficacy and minimize the risks of these drugs in children under 24 months.

10) Studies should be carried out to provide cost-benefit and cost-effective strategies to assist in the control of morbidity due to soil-transmitted helminthiasis in children under 24 months.

18. Recommendations

The practice of excluding women (and adolescents) of childbearing age from drug safety trials has, by default, led to unwarranted restrictions on the treatment of any who might be pregnant. Although it is critical to protect women from unnecessary exposure to any adverse effect of chemotherapeutic drugs, it is nevertheless a violation of women's rights to deny treatment without good reason. If there is no specific contraindication, adolescent girls and women should be offered the opportunity to have the best available treatment while being informed of possible risks.

Schistosomiasis

Data are now available to show that:

(i) women of childbearing age (including pregnant women) are at considerable risk of morbidity in areas endemic for schistosomiasis;

(ii) clinical, experimental or theoretical evidence of reproductive toxicity (clinical, experimental and theoretical) of praziquantel is lacking and there is no reason to believe that its safety is different in pregnancy;

(iii) current drug policies place women of childbearing age in schistosomiasis endemic areas at considerable disadvantage.

It is therefore recommended that:

1) Given the special schistosome-related morbidity of women worldwide, and the beneficial effect of praziquantel treatment:

   a) women of childbearing age should not be excluded from population-based chemotherapy programmes for schistosomiasis; and
   b) pre- and post-pubescent females should be included in all schistosomiasis control strategies and specific steps taken to guarantee coverage.

2) All pregnant and lactating women with schistosomiasis should be offered immediate treatment.

3) Pregnant and lactating women living in areas highly endemic for schistosomiasis, where population-based chemotherapy is employed, should be included and offered treatment.

4) In schistosomiasis endemic areas where universal chemotherapy is not implemented, women of childbearing age (including those pregnant and lactating) should be considered as a high risk group for morbidity.

Soil-transmitted helminthiasis

The benzimidazoles, albendazole and mebendazole (like levamisole and pyrantel) can be safely used in children aged 12 to 24 months. In these children the recommended dose of albendazole is a single dose of 200mg. The recommended dose of mebendazole is either a single dose of 500mg or 100mg twice a day for 3 days.

Pharmacovigilance

WHO should encourage control programmes using PZQ in pregnant women to collect data on the outcome of pregnancy for mother and infant in sufficiently large numbers. These data should be compared with the expected incidence of fetal abnormalities and other negative birth outcomes in the populations concerned.

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Glossary of key terms and abbreviations used in the report

ADI
acceptable daily intake
defined by international and national regulatory committees as the amount of substance occurring in food which can be safely consumed each day for life.

adolescence
the events between puberty (period when secondary sexual characteristics begin to develop and the capability for reproduction is attained) and the completion of physical growth.

ALB
albendazole

CNS
central nervous system

deworming
use of anthelminthic drugs in an individual or in a public health programme.

efficacy
a measure of the therapeutic effect of a drug under ideal conditions.

end organ morbidity
morbidity caused exclusively by schistosomiasis, including hepatic fibrosis, urinary obstruction and bladder cancer.

fetus (foetus)
the developing young in the uterus, specifically the unborn offspring in the postembryonic period, in humans from 7 to 8 weeks after fertilization until birth.

genetic toxicity (genotoxicity)
the production by some chemicals, including certain drugs, of damage to the genetic apparatus of cells. The principal types of genetic damage are:

- point mutation: focal damage to DNA (by an effect on nucleotides)

- chromosomal damage: an effect on the integrity of the structure of chromosomes. It is sometimes called "clastogenicity" because it is commonly seen as a disruption of chromosomes during cell division.

Aneuploidy is a further type of genotoxic action affecting chromosomes. During cell division it results in unequal distribution of the paired chromosomes into the two daughter cells, resulting in an aneuploid (unequal) number of chromosomes in each cell.

Consequences of genotoxicity**:** point mutations and chromosomal damage to somatic cells may be associated eventually with the development of cancer, and, in general, genetic damage in germ cells risks harmful effects in subsequent generations. Aneuploidy may result in various severe and ultimately fatal diseases in the next generation. The dose of a compound causing point mutations and structural chromosome aberrations is related to the frequency of occurrence of these effects but not to their severity, and there is no threshold dose. Aneugens (substances causing aneuploidy) display a very different dose response relationship, as they show a clear threshold of exposure, below which no harmful effect can be detected, in vitro or in vivo, whereas greater exposure results in increasingly harmful effects.

GSH
Glutathione S - transferase

HIV
human immunodeficiency virus

IDA
iron deficiency anaemia.

incidence
the number of new cases of infection appearing in a population in a given period of time.

intensity
the number of worms (measured directly or indirectly) per infected person (worm burden).

LEV
levamisole

MBD
mebendazole

morbidity
clinical or sub-clinical consequences of infections or diseases that affect an individual's well-being.

mutagen
an agent capable of inducing a genetic mutation (permanent change in the DNA found in an individual's chromosomes).

NOAEL OR NOEL
no observed adverse effect level. The highest dose in a toxicity test at which no adverse effect was found. It includes both toxic actions and any excessive therapeutic or other pharmacological action.

PD
pharmacodynamics: study of the effects of drugs at the cell or receptor level, including biochemical, physiological and other mechanisms.

pharmacovigilance:
the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem in clinical practice.

PK
pharmacokinetics - the behaviour, absorption, distribution, localization in tissues, biotransformation, and excretion of drugs and their metabolites.

prevalence
the number (usually expressed as a percentage) of individuals in a population estimated to be infected with a particular species of worm at a given time.

PYR
pyrantel

PZQ
praziquantel

risk group
those identified to be at risk of morbidity and mortality as a result of infection with schistosomes and soil-transmitted helminths. Such groups include preschool children, school-age children, pregnant women and workers with occupations involving contact with fresh water for schistosomiasis or with soil for hookworms (such as miners and tea pickers).

subtle morbidity
morbidity attributable to either schistosomiasis or soil-transmitted helminths that is not normally identified in the clinical case definition for that infection such as anaemia, growth impairment, decreased cognitive and work performance.

TBW
total body water as a percentage of body weight that changes with age from about 78% (new born) to about 60% (after one year).

teratogen
a drug, chemical, or other agent or influence causing physical defects in the developing embryo.

Appendix I

Review papers

Author	Paper presented
Dr S. Awasthi	*Benefits of albendazole and mebendazole in children less than 2 years of age*
Professor A. Dayan	*Albendazole, mebendazole and praziquantel: Review of non-clinical toxicity and pharmacokinetics*
Professor P. Folb	*Global risk analysis of using praziquantel in pregnant and lactating women, and albendazole or mebendazole in children under 24 months*
Dr M. Hanisch	*Notified inadvertent use of praziquantel in pregnant and lactating women, with recorded adverse effects*
Dr J. Horton	*Albendazole: Report on safety*
Professor R. Olds	*Administration of praziquantel to pregnant and lactating women: Risk/benefit of treating pregnant women with praziquantel*
Dr P. Vanparys	*Notified inadvertent use of mebendazole in children under 24 months, with recorded adverse effects*

Appendix II

Extracts from *WHO Model Formulary 2002*
Mary R. Couper, Dinesh K. Mehta, eds.
Geneva, World Health Organization, 2002
ISBN 92 4 154559 3

albendazole

Group: Intestinal anthelminthics

Chewable tablets: albendazole 200 mg, 400 mg

Uses: ascariasis, hookworm infections, strongyloidiasis, enterobiasis, trichuriasis, trichostrongyliasis and capillariasis; cestode infections; tissue nematode infections; filariasis

Precautions: **pregnancy:** contraindicated in cestode infections; first trimester: avoid in nematode infections

Dosage: for ascariasis, hookworm infections, enterobiasis, and trichostrongyliasis, *by mouth*, ADULT and CHILD over 2 years, 400 mg as a single dose

for trichuriasis, *by mouth*, ADULT and CHILD over 2 years, 400 mg as a single dose (for moderate infections) or 400 mg daily for 3 days (severe infections)

Adverse effects: gastrointestinal discomfort, headache

levamisole

Group: Intestinal anthelminthics

Tablets, levamisole (as hydrochloride) 40 mg, 50 mg, 150 mg

Uses: ascariasis, hookworm, and mixed ascariasis with hookworm infections; malignant disease

Contra-indications: breastfeeding

Precautions: **pregnancy**: third trimester: avoid
interactions: consult manufacturer's literature

Dosage: ascariasis, hookworm, and mixed ascariasis with hookworm infections, *by mouth*, ADULT and CHILD 2.5 mg/kg as a single dose; in severe hookworm infection, a second dose may be given after 7 days

Adverse effects: abdominal pain, nausea, vomiting, dizziness, and headache

mebendazole

Group: Intestinal anthelminthics
Mebendazole is a representative benzimidazole carbamate derivative anthelminthic. Various drugs can serve as alternatives

Chewable tablets, mebendazole 100 mg, 500 mg

Uses: ascariasis, hookworm infections, enterobiasis, trichuriasis, and capillariasis; cestode infections; tissue nematode infections

Precautions: **pregnancy**: toxicity in *animal* studies; contraindicated in cestode infections
first trimester: avoid in nematode infections.
interactions: Cimetidine: metabolism of mebendazole possibly inhibited (increased plasma concentration)

Dosage: ascariasis, *by mouth*, ADULT and CHILD over 2 years, 500 mg as a single dose *or* 100 mg twice daily for 3 days

hookworm infections, trichuriasis, *by mouth*, ADULT and CHILD over 2 years, 100 mg twice daily for 3 days; if eggs persist in the faeces, second course after 3-4 weeks; alternatively (especially for mass treatment control programmes), *by mouth*, ADULT and CHILD over 2 years, 500 mg as a single dose

Adverse effects: gastrointestinal disturbances, headache, and dizziness

pyrantel

Group: Intestinal anthelminthics

Chewable tablet, pyrantel (as embonate) 250 mg
Oral suspension, pyrantel (as embonate) 50 mg/ml

Uses: ascariasis, hookworm infections, enterobiasis, and trichostrongyliasis; tissue nematode infections

Precautions: **pregnancy**: safe use in pregnancy has not been established
liver disease (reduce dose)

Dosage: ascariasis, trichostrongyliasis, *by mouth*, ADULT and CHILD 10 mg/kg as a single dose

hookworm infections, by mouth, ADULT and CHILD 10 mg/kg as a single dose; in severe infections, 10 mg/kg daily for 4 days

Adverse effects: mild gastrointestinal disturbances, headache, dizziness, drowsiness, insomnia, rash

praziquantel

Group: Trematode infections

Tablets, praziquantel 600 mg

Uses: intestinal schistosomiasis; urinary schistosomiasis; cestode infections; intestinal flukes, liver flukes, and lung flukes

Contra-indications: ocular cysticercosis

Precautions: **pregnancy**: *T. solium* infections in pregnancy should be treated immediately; if immediate treatment not considered essential for fluke infections or shistosomiasis, treatment should be delayed until after delivery
breastfeeeding: (avoid during and for 72 hours after treatment); areas endemic for cysticercosis - possible oedematous reaction
interactions: Carbamazepina: plasma-praziquantel concentration reduced; Dexamethasone: plasma-praziquantel concentration reduced; Phenytoin: plasma-praziquantel concentration reduced

Dosage: schistosomiasis, *by mouth*, ADULT and CHILD over 4 years 40-60 mg/kg as a single dose; alternatively 3 doses of 20 mg/kg on one day at intervals of 4-6 hours

Intestinal fluke infections, *by mouth*, ADULT and CHILD over 4 years, 25 mg/kg as a single dose

Liver and lung fluke infections, *by mouth*, ADULT and CHILD over 4 years, 25 mg/kg 3 times daily for 2 consecutive days; alternatively 40 mg mg/kg as a single dose; treatment may need to be extended for several days in paragonimiasis

Adverse effects: abdominal discomfort, nausea, vomiting, malaise, headache, dizziness, drowsiness, rectal bleeding; rarely hypersensitivity reactions, including fever, pruritus, eosinophilia (maybe due to dead and dying parasites)