



## COMMITTEE FOR VETERINARY MEDICINAL PRODUCTS

### AQUA LEVICI

#### SUMMARY REPORT

1. *Aqua Levici* is the water of the natural mineral spring "Strong Water" in the mountain area of Ticino/Italy. The water is acidic due to its content of sulfuric acid. *Aqua Levici* contains some trace elements like arsenic (up to 10 mg/l), copper (around 50 mg/l) and iron (more than 1000 mg/l). The water is intended for intramuscular and subcutaneous injection to food producing species at doses of up to 10 ml. This is corresponding to doses of approximately 0.1 mg (0.2 µg/kg bw) arsenic, 0.5 mg (1 µg/kg bw) copper and 10 mg (20 µg/kg bw) iron for large animals (e.g. 500 kg bw). Dosing may be repeated but a fixed dosage schedule is not recommended. The original spring water is corresponding the homeopathic dilution 1:10. The use follows the principles of homeopathic therapy where animals are diagnosed on basis of the individual pattern of clinical signs. *Aqua Levici* is also used in human anthroposophic preparations.
2. Specific pharmacological and toxicological studies for *Aqua Levici* are not available. Iron and copper salts, though contained at relatively high levels in *Aqua Levici*, are considered of no specific concern because absolute amounts of these elements in the injectable dose are negligible compared to normal dietary uptake and body stores in animals. Iron and copper salts which are used in conventional veterinary medicine at considerably higher doses have already been recommended for inclusion into Annex II of Council Regulation (EEC) No 2377/90. Possible health-related concern of *Aqua Levici* may arise from its particular content of the element arsenic far exceeding that of normal mineral waters (less than 50 µg/l).
3. The element As is ubiquitous in the natural environment. Arsenic can exist in various inorganic trivalent (As III) or pentavalent (As V) forms and as organic compounds. Water soluble inorganic arsenicals are well absorbed from the gastro-intestinal tract with over 90% while absorption and bioavailability of natural organic forms is generally poorer. Arsenic is widely distributed to all body compartments with highest concentration in skin and other keratin rich tissues. Metabolism of inorganic arsenicals is mainly by methylation of the element to organic mono- and dimethylated forms. Excretion of arsenic in form of salts and organic metabolites in humans is predominantly via urine with about 50 to 80% of a dose eliminated within a few days.

4. The toxicity of arsenic has been extensively investigated. Oral LD<sub>50s</sub> for inorganic As (III) and As (V) compounds were reported with 10 to 300 mg/kg bw in laboratory species. The lethal dose for humans is about 70 to 180 mg. Naturally occurring organically bound arsenic is far less toxic. Adverse health effects have been mainly associated with inorganic arsenic's: Chronic exposure to elevated arsenic levels can lead to peripheral and central nervous system toxicity, diseases of the skin, the cardiovascular system and internal organs. There is evidence from epidemiological studies that long-term exposure can cause skin cancer in human but also neoplasms of lungs and liver. Arsenic (III) and (V) inorganic compounds have been shown to be potent clastogens in a variety of mammalian cell systems but arsenic compounds were inactive or only weak in their ability to induce gene mutations. The provisional tolerable weekly intake (PTWI) for inorganic arsenic as recommended by the WHO is 150 µg of As/person/day (about 1000 µg/person/week). The upper limits established for arsenic in drinking water are 50 µg/l (WHO) and 10 µg/l (EC), respectively.
5. On the other hand, there is some indication that arsenic in small quantities might be an essential trace element for mammals and birds (possible human requirement was estimated with 12 to 25 µg/person/day). The usual daily intake of humans of total inorganic and organic arsenic via diet and drinking water was estimated with up to 100 to 150 µg/person/day. Arsenic in inorganic and organic forms is also permanently present in feedstuff and drinking water of food-producing animals: Normal physiological concentrations in the edible tissues were reported in the range of 5 to 100 µg/kg in meat (muscle less than liver and kidney), 10 to 50 µg/kg in milk and 10 to 100 µg/kg in eggs. There may be considerably more than 1000 µg/kg in marine fish. In cereals, vegetables and fruits the concentrations of the element are in the range from 30 to 1000 µg/kg. Arsenic was found not to significantly accumulate in the edible tissues with dietary concentrations kept lower than 2 000 µg/kg feed (dry matter weight) and 200 µg/l in the drinking water.

When compared to these normal background levels of dietary arsenic exposure and the physiological turnover rates of the element or the normal steady state levels in tissues, the minor dose of 100 µg As/animal (0.2 µg As/kg bw) applied with *Aqua Levici* treatment was considered insubstantial in terms of residues and additional arsenic burden of food-producing animals and the human consumer of animal derived food.

## Conclusions and recommendation

Having considered:

- *Aqua Levici* is used in a small number of individual animals for non-regular treatment in accordance with the principles of homeopathic therapy,
- the animals are unlikely to be sent for slaughter during or immediately after treatment,
- small quantities of specific trace elements like arsenic, iron and copper used in connection with *Aqua Levici* treatment are negligible in comparison with natural dietary exposure levels and normal steady-state concentrations in edible tissues of food producing species;

the Committee for Veterinary Medicinal Products concludes that there is no need to establish an MRL for *Aqua Levici* and recommends its inclusion in Annex II of Council Regulation (EEC)

No 2377/90 in accordance with the following table:

| Pharmacologically active substance(s) | Animal species             | Other provisions                                                                                           |
|---------------------------------------|----------------------------|------------------------------------------------------------------------------------------------------------|
| <i>Aqua Levici</i>                    | All food producing species | For use in homeopathic veterinary medicinal products prepared according to homeopathic pharmacopoeias only |