

VPC consideration and comments on the Consultation responses to the Draft Veterinary Products Committee Report of the Risks Associated with the Use of Hormonal Substances in Food Producing Animals

Responses to VPC Working group on Hormones

Introductory remarks to responses:

Following the Consultation period on the Report of the VC on Hormones, and the presentation of the Report at the VPC Open Meeting on the 16 November 2005, we have received 17 responses from organisations and individuals for which we are grateful.

Many of the comments received are generally welcoming and supportive of the Report and its findings. Some seemed to be based on a misunderstanding of the role of the VPC and the specific remit of the Working Group (WG). In others, there appears to be a misinterpretation of the presentation of the conclusions and underlying opinions expressed in the Report, or a selection of particular elements of the Report which support their case without acknowledgment of the countering arguments which also appear in the Report. We would stress that this is a complex issue which requires the Report to be considered in its entirety.

There did not seem to be a challenge of the fundamental science within the Report. A number felt that the conclusions were potentially ambiguous in that we concluded that the “weight of evidence” at present, does not indicate that consumers would be at an added measurable risk from eating meat from animals receiving growth promoters, but that at the same time, noting that there were still important gaps in our knowledge and areas of uncertainties for the growth-promoting substances under consideration. We do not feel overall that these two statements are incompatible.

To clarify the role of the WG and the VPC, it should be understood that it is the function of this Committee, and its Working Groups, to give scientific advice. This includes noting gaps in knowledge and uncertainties. In the case of the Working Group on Hormones, it was to give scientific advice, including a risk assessment as far as the science would allow, to the VMD who then have the responsibility to advise Ministers, as appropriate, on any required risk management measures.

The VPC and its Working Groups have no mandate to undertake risk management on behalf of the public. They are neither civil servants nor politicians who are paid or elected respectively and who have such responsibilities. However, the VPC and the WG in this Report have deliberately drawn attention to a number of risk management issues such as the use of the precautionary principle, and the therapeutic versus the non-therapeutic use of hormonally active substances and animal welfare issues. The Report also repeatedly draws attention to gaps in knowledge and areas of uncertainty.

Overall, the WG recommend to the VPC that none of the comments received were such to alter their conclusions and opinions. In order to maintain transparency, we propose to leave the Report in its entirety but attach to it, as an Appendix, all received comments as well as comments from the WG where appropriate. In the case of one response, we have added some information based on a review of two additional papers in the area of environmental risk assessment. These add a little further information, but do not change the conclusions in the Report.

Although comments made on risk management issues do not alter the conclusions reached, it is hoped that they will be useful to regulators in any future decision making process and implementation.

It is noted, for completeness, that one of the Working Group members is also a signatory to one of the submitted responses (the Food Ethics Council).

There were one or two general issues raised by a number of responses that we would like to deal with first.

The report is only about the use of hormonal substances as growth promoters – it is true that these substances are being used for growth promoting purposes in some countries outside the EU, and the safety of meat from such animals needs to be assessed. The use of hormonal substances for growth promotion has been banned since the late 1980's. There is also a ban on importing meat from treated animals. The VPC recognises that this will remain the case.

However, substances such as oestradiol have other uses in animal medicine. For example, individual cows can be treated to improve their fertility (zootechnical uses) and therapeutically for conditions, such a pyometra. Such therapeutic treatments have clear animal welfare benefits.

Effects on animal welfare not assessed – it is true that the report does not assess effects on animal welfare. This is not because it is not important. Rather this aspect was outside of the remit of both the SCVPH Opinion and the VPC Report. However, whenever a substance is put forward for authorisation this would form a part of the assessment.

Some will be aware that recombinant bovine somatotropin (a hormonal substance that encouraged larger yields of milk) was refused authorisation. This was because of concerns over animal welfare and not on human safety grounds..

1. Fiona Bottrill, Wolverhampton City Council

Asked for clarification of the conclusions in the report, to which we responded directly.

2. Tim Brigstocke, Royal Association of Dairy Farmers

We are pleased that they support the report and share their view that safe food is available to consumers.

3. Ms Kate Burnaby, Stock 1st Veterinary and Livestock Services

The VPC note the concerns over the loss of oestradiol-based medicinal substances.

4. Mike Daniels, Deer Commission for Scotland

Made no comments

5. Alistair Donaldson, Scottish Association of Meat Wholesalers

The VPC agrees that consumer confidence in meat is an important issue. There are trade issues linked to the use of hormonal substances for some uses, but this is beyond the remit of the report.

6. Don Grant

Raised some technical questions, which were answered directly.

7. Ms Lucy Harris, Foodaware (an umbrella group of Consumer Organisations on food safety, nutrition and standards)

The VPC notes the concerns over:

- animal welfare;
- the use of the precautionary principle; and
- mixtures of substances and the WiGRAMP report.

These are addressed above. Foodaware has expressed its view over political-economic pressure from the USA. This is outside of the remit of the report.

The VPC notes Foodaware's concerns over the data gaps, which the report flags up. The report also clearly states that further research is needed before definitive risk assessments can be made for oestradiol and the five other hormonal substances.

8. Dr Esther Heller, Food Standards Agency

The VPC is pleased that following the Food Standards Agency's (FSA's) independent assessment of the current evidence it is in broad agreement with the conclusions of the report.

In particular we note that the FSA supports the VPC's view that the weight of evidence available indicates that it is very unlikely that the presence of residues of 17 β -oestradiol in meat from treated animals would significantly increase the risk of adverse effects in consumers unless an active implant site is ingested. Also that the data gaps preclude a definitive risk assessment of the six hormonally active substances.

We note that the Committee on Mutagenicity of Chemicals in Food, Consumer Products and the Environment (COM) supports the VPC's conclusion that there is sufficient evidence to conclude that any genotoxicity of oestradiol is likely to have a threshold because of the body's natural defence mechanisms.

We agree the FSA's contention that all relevant data, including unpublished data owned by companies, should be considered.

We note the view of the COM that zearalenone, a metabolite of zeranol should be considered as being potentially genotoxic. We would welcome further research on this.

9. Peel Holroyd & Associates

The VPC agree that age factors need to be considered

10. Susan Knox

Susan Knox suggested that the precautionary principle should be applied as there were data gaps. We have indicated that it is for regulators to determine the appropriate risk management measures and for them to explain how they are interpreting the precautionary principle in reaching these decisions.

We note that girls in both Europe and the USA are maturing earlier. Therefore, aspects other than pattern of use of hormonally active substances could be responsible.

(Susan Knox is also the key signatory for Foodaware's submission above.)

11. Ms Jeanette Longfield, Sustain the Alliance for Better Food and Farming

Sustain raise the issues of the precautionary principle and animal welfare that has been dealt with elsewhere. Sustain also raise the issue of 'cocktails' of administered substances from a range of animal products. As we have stated elsewhere in our response, the WiGRAMP¹ report concluded, based on literature together with information supplied by stakeholders, that there is limited exposure of humans to multiple residues and that such exposure

¹ Information on assessing the possible effects of mixtures of pesticides and veterinary medicines can be found on the FSA website - <http://www.food.gov.uk/safereating/pesticides/pestmixbranch/>

occurs at low levels, at least through food. However the group also indicated that further research should be undertaken.

Sustain raise the trade dispute between North America and Europe. This was outside the remit of the report and so was not considered by the Working Group.

12. Dr Tom Macmillan, Food Ethics Council

Welfare Concerns important

Agree that regulatory authorities in the EU would need to look closely at any adverse effects on animal welfare of any medicinal product. This was the case for recombinant Bovine Somatotropin, where the product was banned because of animal welfare concerns, rather than concerns about effects on human health.

Risk management not for the VPC

We do not agree that the VPC Report should state how the precautionary principle should be applied. This is a risk management issue which is for the regulatory authorities to address. The Report will assist them in making such decisions by providing as much information as possible and pointing out the gaps in the evidence to help underpin the application of the advice.

Balanced report

We do not agree that the Report is ambiguous. We believe it balances the current evidence and highlights the uncertainties. The Report has had to deal with a complex issue and attempts to set out the evidence and arguments in an even-handed fashion.

We believe the two statements that

- 'the weight of current evidence at present available suggests that likely levels of human exposure to hormonally-active substances in meat from treated animals would not be sufficient to induce any measurable effect'; and
- the Group acknowledges there are important gaps in the evidence base that preclude producing a definitive risk-assessment for 17 β -oestradiol and the five other hormonally active substances';

are balanced and equally stated.

Cocktail Effect

As stated earlier, we are aware that work is in progress to assess any synergistic effects between particular substances. It should be noted that the WIGRAMP report found there was little evidence at present. We would be grateful for the reference indicated in the text.

13. Janice Milne, Scottish Environment Protection Agency

Made no comments

14. Ms Patience Purdey, National Council of Women of Great Britain

We are pleased that the NCW support the VPC's conclusions on the data gaps and uncertainties that exist and the importance of a structured approach to fill these, so allowing a fuller risk assessment. We agree their conclusion that regular reviews of new data would be helpful as this becomes available. We also note the risk management measures that the NCW recommend in dealing with any risks associated with the use of hormonal substances.

The NCW informed us of a number of questions raised by their 'Biotechnology 2000' paper and the Royal society paper on endocrine disrupting chemicals:

- **Are residue levels in countries using hormone growth promoters at an acceptable level?**– it is illegal to export meat from animals treated with hormonal growth promoters to the EU. However, as acknowledged in the report, any residues from such use of natural hormones are difficult to detect, as the concentrations found are no higher than for those from untreated meat.
- **Is there a cocktail effect?** – this is an area that is covered elsewhere in this response.
- **Could the extra hormones affect human DNA?**– any application for use of such substances would have to include data to show that there would be no adverse effects on human DNA
- **Is there a safe withdrawal period before slaughter?**– any application would have to identify a withdrawal period that would ensure consumers are not exposed to unacceptable residues.
- **Do hormones used in fish-farming get into the water downstream** – the VPC have taken advice on this. The view is that this type of treatment is relatively rare, and is required to be carried out in a tank isolated from the watercourse. An environmental assessment is carried out on all new medicinal substances.

Dairy Cattle

The NCW also expressed concern about drinking milk with hormonal residues. It has always been a normal part of dairy husbandry to take milk from pregnant cows. Consequently for part of the lactation cycle it is likely that there will be detectable residues of oestrone sulphate.

We do not believe that dairy cows would be treated with hormonal growth promoters. There is a possibility of some cows receiving treatment with PRID, which contains 17 β -oestradiol, to improve the fertility of the cow. However, these treatments will not be allowed after October 2006.

The removal of the Over Thirty Month Scheme (OTMS) is a separate issue to milk production and is covered in the report. Now that the

OTMS has been lifted these older cattle will be eligible to re-enter the food chain. At present we do not know what demand there is for meat from these older animals. It is our estimate that 25% of such older cows could be pregnant, and so possess elevated concentrations of some hormonal substances. However, this would have also been the situation before the OTMS was introduced in 1996.

Levels of likely exposure

The VPC based their assessment that likely levels of exposure would be unlikely to result in any measurable physiological effect was based on the currently available knowledge. For example the VPC noted that a doubling of serum oestradiol concentration could result in an increase in risk of breast cancer in post-menopausal women of a factor of 1.25. Based on the data from Arnold (1999) the possible increase in serum concentration in those most exposed to residues would be only 0.01%. This increment is approximately 3 orders of magnitude below the most sensitive assays available and below any concerns related to breast cancer risk.

Further research

The VPC acknowledge that the NCW is right to say that affordability should not be a restricting factor in seeking the key information that is needed to perform a risk assessment on the hormonal substances.

15. Alsaneh Roberts, Country Land and Business Association (CLA)

We are glad that the CLA welcomed the report and agree that decisions should be based on sound science. We also endorse their view that international collaboration to answer the questions raised would be useful.

16. Richard Young, Soil Association

Animal Welfare

We agree that no consideration was given to animal welfare in the Report for the reasons given above. However, we would also like it noted that the WG consider animal welfare to be an important issue, but that this would be automatically considered in any risk management decision.

Environmental Effects

We are grateful for the Soil Association for bringing to our attention two papers on the possible environmental effects of hormonal substances that were published after our section on this was drafted. Dr Mark Crane provided expertise to the VPC Working Group on environmental issues and has considered the two papers. We detail his response below.

Orlando et al. (2004) show that wild fathead minnow (*Pimephales promelas*) collected from below a cattle feedlot were demasculinised, and there was some evidence of female defeminisation. The authors

concluded that future studies are needed to examine fish exposed to slurries of manure from treated and untreated animals to identify the biologically active agents, whether natural or pharmaceutical in nature." This was because they were unable to identify the androgenic components of feedlot effluent that caused these biological effects, which could have been due either to natural androgens found in faecal material or to androgenic pharmaceuticals used in growth implants.

The widespread use of these implants in cattle reared in the US meant that the researchers were unable to collect fish below feedlots where implants were not used, and so were unable to separate these two potential causes of reproductive effects in fish.

Soto et al. (2004) measured androgenic and estrogenic activity using screening bioassays and chemical analysis in surface water that received cattle feedlot effluent, including sites sampled in the study by Orlando et al. (2004). They found an increase in both androgenic and estrogenic activity in screening bioassays and were also able to identify estrone in water samples.

Unfortunately, samples from reference sites also displayed hormonal activity, possibly because of manure spreading near these sites. These well-performed studies provide evidence to suggest that use of hormonal implants in cattle may be associated with increased concentrations of hormones in surface waters receiving effluent from cattle feedlots, and that this may in turn be associated with reproductive effects on resident fish species.

The Working Group believes results from these studies are insufficient to demonstrate cause and effect. Research to establish a source-pathway-receptor linkage is required. The SCVPH should provide specific criteria for such research so that their decision is based upon a fair interpretation of the precautionary principle. It is assumed that if the re-introduction of growth-promoting substances for use within the EU were considered in the future, then a full environmental risk assessment would need to be conducted according to good current scientific practice

Inaccuracies in the Soil Association's Submission

There are a number of factual inaccuracies in the Soil Association's comments. The Soil Association states:

- **'that the lack of a definitive risk assessment will be given less prominence in the final report'**. This is not correct; there is no suggestion that the introduction to this section will be changed to reduce this statement's prominence.
- **That the statement in the VPC report that 'based on the evidence at present available suggests that the likely levels of human exposure to hormonally active substances in meat treated animals would not be sufficient to induce any**

measurable physiological effect.’ cannot be supported by the evidence in view of the data gaps that exist. The VPC clearly state that this is based on **evidence at present available**. The VPC have made clear statements on what the data gaps are and what extra work would be useful. Once this data is generated it would become part of the **evidence at present available** and would have to be assessed.

- **‘There is growing evidence for the ‘cocktail effect’.** The VPC is unaware that there is any growing evidence for the cocktail effect. Indeed, the WiGRAMP report on mixtures of chemicals concluded:
 - Evaluation of the literature together with information supplied by stakeholders has shown that there is limited exposure of humans to multiple residues and that such exposure occurs at low levels, at least through food. There are no substantiated accounts of adverse reactions to such exposures except under laboratory conditions. Nevertheless the nature and extent of combined exposure, together with the likelihood of any adverse effects which might result, should be evaluated when carrying out risk assessment.

We are aware that an extensive research programme is underway, funded by the FSA, following the recommendation in the WIGRAMP report. These findings will inform the debate on the “cocktail effect”.

- **‘The VPC rejects the conclusions of the SCVPH Opinion’.** In fact the VPC agrees with many of the conclusions of the SCVPH, for example:
 - “that the current state of knowledge does not make it possible to give a quantitative estimate of the risk to consumers”;
 - there are important gaps in the evidence base that preclude producing definitive risk assessments for 17 β -oestradiol or the other five hormonally-active substances
 - the VPC consider it prudent to consider 17 β oestradiol a complete carcinogen until more substantial evidence for the mode of action is obtained;
 - the importance of considering lipoidal esters of oestrogen in future studies of the possible passage of oestrogen in implants through cattle to humans. The bioavailability and metabolism of lipoidal esters following ingestion should be investigated to allow the biological significance of the oestrogens to be assessed;
 - No new data regarding testosterone and progesterone relevant to bovine meat or meat products are available.
 - The data presented on zeranol and trenbolone tested their mutagenic and genotoxic potential in various systems with different endpoints. Both compounds exhibited only very weak effects.

- **‘that in contrast to the VPC the SCVPH looks at the latest evidence’.** In fact the SCVPH referenced mostly the 17 studies it had commissioned and the papers written from them. The view of the VPC was that these reports and papers gave very little new evidence.

The VPC, however, looked at **all** of the reports and papers the SCVPH cited plus many other recent papers, as can be seen from the two reference lists in the report.

- **that the VPC report’s Executive Summary makes no mention of the possible risk to pre-pubertal boys.** This is not correct - one recommendation in the Executive Summary is:
 - To carry out studies to confirm whether the ADI for pre-pubertal boys could be exceeded if they consumed a standard² 500g portion of meat from an animal that had been treated with a number of hormonal implants. If confirmed this would be of concern.

Starting point for the report

The Soil Association suggested that the VPC started from the Lamming Committee and the WHO/FAO Joint Expert Committee on Food Additives (JECFA). It is not clear what they mean. Certainly we did not base our reasoning on these Committees’ findings. Having said that, it is true that if we look back, nearly all other expert committees have concluded that any risks to consumers of consuming meat from animals treated with hormonally active substances are small. For example:

- Committee for Medicinal Products for Veterinary Use (CVMP), the EU’s own Committee for assessing safety data on substances submitted for authorisation as veterinary medicines;
- JECFA, as stated in the Soil Association’s submission;
- The VPC Report in 1999; and
- Chemical Review and International Harmonisation Section Office of Chemical Safety Therapeutic Goods Administration – who assessed the SCVPH’s 2002 Opinion for the Australian government (http://www.apvma.gov.au/publications/review_HGP.pdf).

17. Jane Virgoe, British Veterinary Association

The VPC is not advocating the reintroduction of particular hormonal substances in food-producing species. As the BVA would know, the use of such substances for growth promotion is banned, but there are current authorisations for substances such as for oestrus synchronisation and

² The JECFA veterinary hypothetical diet assumes daily consumption of 300g muscle, 100g liver, 50g kidney and 50g fat.

fertility uses. There are also authorisations for therapeutic treatments of sick animals.

We accept their concerns that the EU should establish an independent laboratory test to confirm that meat has not been derived from animals produced with the aid of growth promoting hormone implants. The Report draws attention to the need for appropriate analytical procedures to be validated.