

# Risks Associated with the Use of Hormonal Substances in Food- Producing Animals

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**Draft report of the Veterinary Products Committee**

**May 2005**

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# Executive Summary

## Introduction

In April 1999, the European Commission published an Opinion of the Scientific Committee on Veterinary Measures relating to Public Health (SCVPH) on the potential risks to human health from the residues in meat and meat products of hormonally active substances used for growth promotion purposes in cattle, in particular the six hormones, 17 $\beta$ -oestradiol, testosterone, zeranol, progesterone, trenbolone acetate and melengestrol acetate. The SCVPH concluded that risks associated with the consumption of meat from hormone-treated cattle may be greater than previously thought. The Opinion expressed in the SCVPH report were subsequently assessed by a sub-committee of the UK Veterinary Products Committee (VPC), and the European Safety Working Group of the Committee for Veterinary Medicinal Products (CVMP). The VPC sub-committee and the CVMP Working Group reported their evaluations later that year (1999) and both groups were unable to support the SCVPH's conclusions. The UK Government accepted the view of the VPC, although it continued to fulfil its obligation to enforce the EU ban on the use of all hormonally active substances as growth promoters in food producing animals<sup>1</sup>.

In the light of the 1999 evaluations by VPC and CVMP, SCVPH released a review of their Opinion in May 2000; this stated that their original conclusion did not need revising.

In early 1998 the European Commission sponsored 17 research studies to evaluate the health risks posed by eating hormone-treated meat and environmental effects of hormone use. Following completion of these studies, SCVPH released a second Opinion in April 2002 that confirmed the views of the first SCVPH Opinion and concluded that no amendments were justified. In response to this second Opinion, the UK Government asked the VPC to re-examine the scientific evidence for a ban on the use of hormones in food-producing animals, and a sub-committee of the VPC was formed in November 2002 (VPC Working Group on Hormones) to carry out this task. The VPC Working Group findings form the content of this report.

## Terms of Reference

To evaluate the latest Opinion of the Scientific Committee on Veterinary measures relating to Public Health (SCVPH) dated April 2002 and advise on its conclusions, and to advise on whether the latest Opinion of the SCVPH, and the research studies on which it is based, addresses the conclusions reached in the report by the VPC Working Group published in October 1999.

## Overview

Following a critical evaluation of the scientific reasoning and methods of argument adopted in the key papers and studies cited in the SCVPH 2002 Report, the Working Group were unable to support the conclusion reached by the SCVPH that risks associated with the consumption of meat from hormone-treated cattle may be greater than previously thought. The weight of 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 physiological effect<sup>2</sup>. In reaching this conclusion the Group acknowledges there are important gaps in the evidence base that preclude producing definitive risk assessments for 17 $\beta$ -oestradiol or the other five hormonally active substances.

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<sup>1</sup> The use of hormonal growth promoters in food producing animals, including the six hormonal substances covered in the 1999 SCVPH Report, has been banned in the European Community since 1988. Third countries [non-EU countries] are required to guarantee that no animals and no meat coming from animals to which these substances have been administered will be exported to the EU.

<sup>2</sup> As a worse-case example, it has been estimated that a postmenopausal woman eating a kilogram of meat (kidney) with the highest concentration of oestradiol detected (56 ng/kg) would experience an increased oestrogen level of 0.01% of average endogenous production.

## Conclusions and recommendations

1. The Working Group were of the view that human exposure to residues of hormonally-active substances, including growth promoters in meat, could exert biological effects if exposure is at a sufficiently high level. Therefore, the two key issues are:
  - (i) determination of the dose-response for induction of biological effects by the hormonally-active substances in test animals and, ideally, humans in order to identify a Lowest Observable Effect Level (LOEL), and
  - (ii) determination of the level (and range) of the additional human exposure and uptake from eating meat from treated animals.
2. These determinations should be made in adults and in developing (fetal/neonatal) animals and humans to identify the most sensitive index of effect. These effects would be in addition to those occurring naturally due to endogenous hormones.
3. The research so far has provided some, but not all the basic, but essential information outlined above. Without it, no definitive conclusions can be drawn; although the weight of available evidence suggests that likely levels of human exposure to hormonally-active substances in meat from treated animals would not be sufficient to induce any measurable biological effect.
4. Specifically, it is very unlikely that the presence of 17 $\beta$ -oestradiol and its metabolites in meat from treated animals would significantly increase the risk of adverse effects in consumers. This is due to their low concentrations in comparison with those arising from endogenous production and from other dietary sources. Any increase would be likely to be small in the context of the entire food basket.
5. In reaching these conclusions, the Working Group expressed a number of qualifications and reservations based on the current lack of evidence of a risk to humans. These included:
  - all scientific judgements made by the Working Group were based on the assumption that the consumer is exposed to residues at no greater concentrations than those that would be caused by the “correct” or “recommended” use of the exogenous hormones, be it for growth promotion or other permitted zootechnical uses or therapeutic purposes;
  - the Working Group understand that misuse of hormonally-active substances for growth-promotion was more likely than misuse for oestrus synchronisation or therapeutic uses; and
  - substances with hormonal action may be used in combination, both legally and illegally, while the toxicological and safety factors available (e.g. ADIs) only relate to single substances.
  - the Working Group had to decide what to do in the absence of information or where there was uncertainty of interpretation of information. One Member expressed the view that for the substances under consideration, there was a large element of uncertainty, so the precautionary principle should become the primary consideration. The many uncertainties associated with the current lack of knowledge could be addressed by further research where this was both feasible and affordable. The Working Group was unanimous that all uncertainties must be made clear, especially those that were considered crucial in the risk assessment process.

6. As has been noted in this report, and acknowledged in the SCVPH Opinion, there are important gaps in the evidence base that preclude producing definitive risk assessments for 17 $\beta$ -oestradiol or the other five hormonally-active substances. Not all data gaps are equally important for the purposes of risk assessment and the Working Group highlighted a number that could improve future risk assessments. As an example, it would be helpful if the CVMP and JECFA could make available data on pharmacokinetics and metabolism of assessed compounds that were supplied in manufacturers' dossiers. This openness and transparency would allow greater public scrutiny of the facts and confidence in the hazard and risk assessments produced.
7. The Working Group felt that none of the basic issues could be addressed without a structured approach. There was a need to establish precisely the:
  - relationships between the potential use of growth-promoters (including over-use) and concentrations of residues in meat;
  - levels of exposure in consumers (i.e. taking account of intake, absorption, bioavailability and metabolism); and
  - dose-response relationships for the effects of the hormonally-active substances (and their metabolites) in experimental animals or in humans.
  - further data on lipoidal oestrogens, possible bioaccumulation and possible synergistic effects of cocktails of hormonal substances would also be desirable
8. The Working Group noted specific needs:
  - To establish in humans the detailed relationship between systemic exposure to specific hormonally-active substances and the amount of meat consumed from treated animals.
  - To establish in experimental animals the relationship between intake of hormonally-active substances, or their metabolites, and target-organ effects (selecting the likely most sensitive target organ depending on the nature of the activity of the compound). This study to be conducted for adults and then fetal and/or neonatal exposure to be considered.
  - To consider 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.
  - To carry out studies to confirm whether the ADI for pre-pubertal boys could be exceeded if they consumed a standard<sup>3</sup> 500g portion of meat from an animal that had been treated with a number of hormonal implants. If confirmed this would be of concern.
9. The following need to be established in order to improve future risk assessments:
  - the precise relationship between the potential use of growth-promoters and concentrations of residues in meat
  - levels of exposure in consumers

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<sup>3</sup> The JECFA veterinary hypothetical diet assumes daily consumption of 300g muscle, 100g liver, 50g kidney and 50g fat.

- dose-response relationships for the effect of hormonally active substances (and their metabolites) in experimental animals and humans
- the bioavailability, metabolism and possible bioaccumulation of lipoidal esters of oestrogen following ingestion of meat from implanted cattle
- the possible synergistic effects of cocktails of hormonal substances
- a validated technique to detect and assign low residual concentrations of oestradiol in the finished edible products to natural sources or implant residues.

## **Appendix D: Membership and Expertise of the VPC Working Group on Hormones**

### ***Professor Leonard Stephen Levy OBE, BSc, MSc, PhD, FFOM (Chairman)***

Specialism: Toxicology and Carcinogenesis

Professor Levy is currently Head of Toxicology and Risk Assessment at the Medical Research Council Institute for Environment and Health based at the University of Leicester. He is an occupational environmental toxicologist. He trained in cancer research at the Institute of Cancer Research at the University of London and has held teaching and research appointments at the Universities of Aston and Birmingham. He is currently engaged in providing risk assessments to humans from a wide range of environmental and occupational substances. He was appointed to the Veterinary Products Committee in May 2001.

### ***Dr Andrew Bradley MA, VetMB, DCHP, DipECBHM, PhD, MRCVS (RCVS Specialist in Cattle Health and Production)***

Department of Clinical Veterinary Science, University of Bristol - Specialism: Large Animal Veterinary Medicine

Dr Bradley is a Senior Lecturer in Ruminant Production Medicine at the University of Bristol and is an RCVS Specialist in Cattle Health and Production. He is Director of the University of Bristol Farm Animal Practice. His area of research is dairy production medicine, in particular bovine mastitis. Dr Bradley is keen to maximise animal welfare whilst maintaining productivity and food safety using an evidence-based approach. He is a member of the Veterinary Products Committee.

### ***Professor Anthony Dayan LLB, MD, FRCP, FRCPATH, FFOM, FFPM, FIBiol***

Specialism: Mechanistic Toxicology

Professor Anthony Dayan was formerly Professor of Toxicology at Queen Mary and Westfield College, University of London. He has previously been a member of the Veterinary Products Committee, the Medicines Commission and the Committee on Toxicity. His principal scientific interests have included immunotoxicology and functional mechanisms of toxicity.

### ***Professor Mitch Dowsett BSc, PhD***

Specialism: Endocrinology

Professor Dowsett is Professor of Biochemical Endocrinology, Head of the Academic Department of Biochemistry at the Royal Marsden Hospital and Institute of Cancer Research, London. His area of research is breast cancer with particular emphasis on hormonal analyses. His laboratory has provided the oestrogen analyses for regulatory submissions for several new drugs for breast cancer treatment and has conducted analyses from several large epidemiological studies over the last few years. From 2001 – 2003 Mitch was the Chairman of the British Breast Group.

### ***Dr Leigh Henderson BSc, PhD, DIBT***

Specialism: Genetic Toxicology

Dr Henderson is an independent consultant providing advice on general, genetic and occupational toxicology to the consumer goods and chemicals industry. She is also the external programme advisor to the UK Food Standards Agency on colon cancer and diet. She is a EUROTOX registered toxicologist and is a UK-nominated genetic toxicology expert to the OECD. She has conducted

research in the areas of veterinary cytogenetics, transplacental genotoxicity, DNA repair and development of new tests for genotoxicity. Dr Henderson is a member of the Veterinary Products Committee.

### ***Professor Ed Houghton***

Specialism: Analytical Chemist

Professor Houghton joined HFL (formally the Horseracing Forensic Laboratory) in 1974 as a Senior Scientific Officer to establish a Mass Spectrometry Unit. Ed is currently a Director of HFL and Chief Scientist, he has also been appointed as a Visiting Professor in the Department of Chemistry and Physics at Nottingham Trent University. Ed is a fellow of the Royal Society of Chemistry and the Association of Official Racing Analysts and Veterinarians. He has published extensively on drug metabolism and mass spectrometry.

### ***Dr W John McCaughey MA, MS, MVB, PhD, MRCVS, FRAgS***

Specialism: Veterinary Public Health

Dr McCaughey was Deputy Chief Veterinary Research Officer in the Veterinary Science Division of the Department of Agriculture, Northern Ireland. Until his retirement he was also Senior Lecturer in the Faculty of Agriculture and Food Science in the Queen's University, Belfast, where he continues to lecture. He holds a part-time consultancy in cattle breeding in the Agricultural Research Institute for Northern Ireland. Dr McCaughey is a past President of the Association of Veterinary Teachers and Research Workers, of the North of Ireland Veterinary Association and is an honorary member of the Association of Veterinary Surgeons Practising in Northern Ireland. His interests centre on the detection and control of veterinary drug residues in food animals, the detection of natural toxins and on the reproductive performance of farm animal species. He was first appointed to the Veterinary Products Committee in 1998.

### ***Professor Jim Parry***

Specialism: Genetic Toxicology

Professor Parry is Professor of Genetics at the University of Wales Swansea where he heads a research group focusing on the mechanisms of chemically induced mutation. He has a particular interest in the influence of low doses of chemical upon the fidelity of chromosome segregation. Professor Parry is currently a member of the Food Standards Agency's Advisory Committee for Wales and the Medical and Toxicology Panel of the ACP.

### ***Professor Richard Sharpe***

Specialism: Reproductive Sciences

Professor Sharpe heads one of the research teams in the MRC Human Reproductive Sciences Unit in the area of male reproductive health. He has research interests in all aspects of male reproduction and endocrinology, from molecular to clinical, from fetal life through to adulthood. His main research interest is in the role of fetal development in the aetiology of adult human male reproductive dysfunction. He serves/has served on numerous government and other expert committees, grant awarding bodies etc. He was until recently Editor of the International Journal of Andrology and is currently on the Editorial board of Human Reproduction and the Journal of Endocrinology. He is an Academician of the European Academy of Andrology.

### ***Mr John Verrall DBA***

Specialism: Pharmacology and Risk Assessment

Mr Verrall was a pharmaceutical chemist for 50 years, 35 of which he worked in the pharmaceutical industry and was involved in product development, marketing and general management. He has taken a particular interest in the use, misuse and abuse of products in their veterinary and animal health applications and also in risk assessment/risk management and the application of the Precautionary Principle. A former Chairman of the Farm and Food Society, he is now a member of The Food Ethics Council – an independent council for ethical standards in food and agriculture. He represents the Council on the Codex Consumer Group of the Food Standards Agency and at Consumer and Stakeholders' Liaison meetings with the Veterinary Medicines Directorate. He has been a member of the VPC since 2002.

## **Expertise called upon by the Working Group**

### ***Dr Mark Crane BSc, PhD<sup>4</sup>***

Specialism: Environmental Risk Assessment

Dr Crane is an independent environmental consultant, providing advice and training to government and industry. He is an ecotoxicologist interested in the effects of agricultural and industrial chemicals on a wide range of biological systems. He currently works on the risk assessment of contaminated sediments, surface waters and groundwaters, the derivation of environmental quality standards, and the effects of endocrine modulators on aquatic invertebrates. He is a member of the Environmental Panel of the Advisory Committee on Pesticides. He was appointed to the Veterinary Products Committee in 2000.

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<sup>4</sup> Dr Crane was not a member of the Working Group. He was invited to give his expertise on the environmental effects of the use of hormonal growth promoters by correspondence to the VPC Working Group on Hormones. He had full access to all documentation, including the SCVPH 2002 Opinion and was consulted over the draft presented to the VPC.