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COMMITTEE ON CARCINOGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT

POSSIBLE CARCINOGENIC HAZARD TO CONSUMERS FROM INSULIN-LIKE GROWTH FACTOR-1 (IGF-I) IN THE DIET

Background

1. At its meeting on the 20th November 2008, the Committee discussed a paper on "Horizon Scanning 2008" (CC/2008/17). One of the issues raised in this paper was the possible carcinogenic hazard from dietary insulin-like growth factor-1 (IGF-I). A member of the public had contacted the Food Standards Agency (FSA) and the Veterinary Medicines Directorate (VMD) over concerns about the import of dairy produce from countries that allow the use of bovine somatotropin (BST) in cows. The use of BST was said to increase the amount of IGF-I in milk, and there was concern that increased dietary exposure to IGF-I might increase the risk of consumers developing cancer. The concern had been prompted by issues raised in the book "Your Life In Your Hands" by Professor Jane Plant. In the book, the author suggested that consumption of IGF-I in dairy produce could cause increased risks of developing certain cancers, particularly breast and prostate cancers. Furthermore, the author proposed that a diet based on the Chinese diet, excluding dairy produce, would reduce the risk of cancer and would also benefit cancer patients.

2. The COC were informed that, at its meeting in July 2008, the Veterinary Products Committee (VPC) had discussed the allegation that milk from BST-treated cows could increase the risk of cancer in consumers. The VPC reaffirmed the conclusions it reached in 1999, when it had considered an application for marketing authorisation of a veterinary medicinal product that had recombinant BST as its active ingredient. It had been concluded that the administration of BST to dairy cows did not substantially increase the level of BST in milk. However, the VPC could not exclude the possibility that dietary IGF-I might cause cell proliferation of the gut mucosa with the potential to increase the prevalence of carcinoma of the large bowel. Marketing authorisation was not granted for the BST product, partly as a result of concern over animal welfare issues (mastitis, lameness and injection site reactions). Following assessment in 1999 by the European Union (EU) Scientific Committee on Food (SCF), the use of BST was not permitted anywhere in the EU for similar reasons. However, no restrictions were put in place regarding import of dairy products from countries that permit the use of BST. Under the General Agreement on Tariffs and Trade (GATT), the EU is not permitted to ban milk products derived from cows legally treated with BST in other countries (eg. USA and Mexico).

3. The COC observed that concerns relating to dairy products and cancer risk are broader than just IGF-I, and it noted that some health care professionals advise women with breast cancer to avoid eating dairy products. It was suggested that the Secretariat should examine the evidence presented in Professor Plant's book and that, if adequate data are presented, these should be brought back to the Committee for review.

The Author of the Book

4. Information about Professor Jane Plant can be found at her websites: www.janeplant.com and http://www.plantprogramme.co.uk/. She is employed in the Department of Earth Sciences and Engineering at Imperial College, London, as Anglo-American Professor of Geochemistry. She has a degree in geology, a PhD in geochemistry and more than 30 years' experience in the fields of geology and geochemistry. Professor Plant has undergone training in integrated medicine and works as a Locum Consultant Nutritionist at the Dove Clinic for Integrated Medicine, which is based in Twyford, and offers patients a wide range of complementary medicines. Professor Plant is on the Advisory Board of the Dove Clinic and is a director of Breast Cancer Understanding and Prevention (BCUP), a foundation she has established to promote more widespread understanding of the proposed causes of breast cancer that are described in her book "Your Life In Your Hands. She has been a member of several committees including chairing the Advisory Committee on Hazardous Substances (ACHS) from 2001 to 2008.

5. Professor Plant is the author or co-author of several popular science books, including:

- Plant, J.A., 2000, "Your Life In Your Hands: Understand, prevent and overcome breast cancer and ovarian cancer", Virgin Books. Expanded, updated and revised fourth edition, 2007. ISBN: 978 0 75351204 3. Sales >4 million worldwide, translated into 15 languages.

- Plant, J.A. & Tidey, G., 2001, "The Plant Programme: Recipes for Fighting Breast Cancer and Prostate Cancer", Virgin Books. Second edition 2004. ISBN: 0753509520.

- Plant, J.A., 2002, "The No-Dairy Breast Cancer Prevention Program: How One Scientist's Discovery Helped Her Defeat Her Cancer", Publisher: St. Martin's Griffin. ISBN: 0312291671 .

- Plant, J.A. & Tidey, G., 2003, "Understanding, Preventing and Overcoming Osteoporosis", Virgin Books. ISBN: 0753508931.

- Plant, J.A., 2004, "Prostate Cancer: Understand, Prevent and Overcome", Virgin Books. Second edition 2007. ISBN: 1852271884.

- Plant, J.A. & Tidey, G., 2005, "Eating for Better Health: The Plant Programme", Virgin Books. ISBN: 0753509075.

- Plant, J.A. & Stephenson, J., 2008, "Beating Stress, Anxiety and Depression", Piatkus, London.

"Your Life In Your Hands" was Professor Plant's first book outside of the field of geology. In it, she wrote of her experience of having breast cancer and her recovery following diet and lifestyle changes. The book also presented information on dietary factors (including IGF-I) that may affect cancer risk. Following the success of this

book Professor Plant wrote several other books dealing with other diseases, including prostate cancer and osteoporosis, and giving dietary advice and recipes to help people follow the principles set out in her books. The latest edition of "Your Life In Your Hands" has been expanded with the addition of seven update chapters plus an additional chapter reporting the experiences of several people with cancers of the breast, ovary or prostate who have followed the dietary advice given in earlier editions of the books. In 1997, Professor Plant was awarded a CBE for her work on earth sciences and, in 2005, she was made a Life Fellow of the Royal Society of Medicine for her books on cancer.

References Given in the Book

6. The Secretariat has tried to obtain copies of all of the references to IGF-I and its properties that were given in Professor Plant's book. Unfortunately, a few of the cited articles were not found and some of the hyperlinks would not open, but sufficient articles were available to give an indication of the scientific basis of the points of view expressed in the book. The Annex to this paper lists the issues raised in Professor Plant's book in the order in which they are discussed in the book. The references listed in this COC paper and its Annex are given as an alphabetic list at the end of the Annex. The text in italics at the end of each reference indicates where the article is cited in Professor Plant's book. This information is also given in the Annex under the heading "Where in the book?" under each entry for "Issues raised".

7. The cited articles are referenced in an unusual way in the book. References are listed in a section near the end of the book entitled "Notes" which gives numbered references from each chapter: Chapters 1 to 7, followed by Updates to Chapters 1 to 7. Each time an article is cited, it is given a new number. Consequently, some articles are referenced several times under different numbers, sometimes in several different chapters.

8. For each issue raised in the book, the Secretariat has made comments in the Annex to indicate whether the claims made are justified by the information cited in the reference, and in some cases adding some additional information from the cited article that had not been included in the book. Most of the claims made in the book were supported by references. Some references were to peer-reviewed articles in scientific journals, whereas others were to magazine articles, books, lectures and websites.

Scientific Issues Raised in the Book

9. In her book, Professor Plant raised several issues relating to the consumer safety of dietary IGF-I. These are listed in the Annex to this paper, in the order in which the issues were raised in the book. It was suggested that certain dietary factors, particularly high intakes of dairy produce, affect the incidences of various cancers. It was further claimed that, if consumers followed the diet promoted in Professor Plant's books, they would have a reduced risk of developing certain cancers and those already having these cancers could go into remission. A possible mode of action for this was proposed: dairy products and some other foods contain IGF-I; dietary IGF-I might increase circulating levels of biologically-active IGF-I; and this in turn could cause increased growth of cancers. The evidence cited in support of

these claims is examined in the following few paragraphs. (The references are listed at the end of the Annex.)

10. Insulin-like growth factor 1 (IGF-I) is a polypeptide growth factor that is produced mainly by the liver but also by other tissues of the body (Chan, *et al*., 1998). Endogenous levels of circulating IGF-I increase throughout childhood, reaching a peak plasma concentration of approximately 200 ng/mL at about 12 years-of-age in girls and 14 years in boys (Perdue, 1984; Yu and Rohan, 2002). After puberty these levels fall to about a half or a third of the peak value and then gradually decrease with age, with levels in women being generally higher than in men of the same age (Perdue, 1984; Underwood, *et al*., 1980; Yu and Rohan, 2002). Circulating levels of IGF-I can change in different physiological states. They increase in the second half of pregnancy, fall slightly during sleep, and fall during acute fasting and chronic protein-calorie deprivation (Underwood, *et al*., 1980).

11. The book made reference to studies that showed that exposure to IGF-I can cause the proliferation of various cells, including cancer cells. IGF-I was mitogenic *in vitro* in chick embryo fibroblasts (Outwater, *et al*., 1997; Zapf, *et al*., 1978) and in explants of epithelial crypt cells from the adult human duodenum (Challcombe and Wheeler, 1994), and it was claimed that IGF-I was mitogenic in normal and transformed human prostate epithelial cells (Chan, *et al*., 1998). IGF-I has been shown to enhance the proliferation of some cancer cell lines *in vitro* (Choki, *et al*., 1998; De Leon, *et al*., 1992; Grothy, *et al*., 1999; Hankinson, *et al*., 1998; Kobari, *et al*., 1998; LeRoith, *et al*., 1995; Musgrove and Sutherland, 1993; Parisot, *et al*., 1999; Perks, *et al*., 1998; Pollak, *et al*., 1992; Surmacz and Burgaud, 1995; Westley, *et al*., 1998) with 1 ng/mL of IGF-I causing a 4- to 5-fold increase in numbers of MCF-7 human breast cancer cells after 5 to 7 days incubation (De Leon, *et al*., 1992) and 0.765 ng/mL causing a 2-fold increase in cell cycle progression in T-45D human breast cancer cells (Musgrove and Sutherland, 1993). It was noted that IGF-I is a more potent mitogen of breast cancer cells than oestradiol (Pollak, *et al*., 1992). It has been suggested that IGF-I also has a role in the differentiation of cells (Fonfa, 2002; McCusker, 1998). A review article (McCusker, 1998) claimed that IGF-I can cause increases in nutrient transport, protein synthesis and RNA synthesis that can result in increased cell size, differentiation of certain types of cells and increased cell survival, but no details were given. IGF-I also inhibited apoptosis *in vitro* in normal and transformed human prostate epithelial cells (Chan, *et al*., 1998) and in BALB/c 3T3 cells that over-expressed the human IGF-I receptor (Sell, *et al*., 1995). IGF-I also stimulated lipogenesis in fat cells, but it was 110 times less potent at doing this than insulin (Zapf, *et al*., 1978).

12. A complex interaction of physical factors (energy intake, body mass index and physical activity) and levels of hormones (including insulin, growth hormone (somatotropin), oestrogen, testosterone, T3 and T4) control the rate of secretion of IGF-I by cells (Holly, *et al*., 1999; Yu and Rohan, 2002). Sex steroid hormones can also affect the activity of IGF-I: by directly affecting pituitary secretion of growth hormone or by altering levels of IGF-binding proteins (Holly, *et al*., 1999). Oestrogens can increase the sensitivity of breast cancer cells to IGF-I (Westley and May, 1994). Binding of hormones to the androgen receptor switches off production of the IGF-I binding protein, IGFBP-3, resulting in an increased amount of free IGF-I in the bloodstream (Marcelli, *et al*., 1995). IGF-I can cause increases in the levels of some

hormones, for instance, when IGF-I was used to treat Laron dwarfism, patients experienced an increase in male hormone levels (Fox, 2002). Professor Plant states in her book that a combination of potentially interacting mechanisms involving IGF-I effects on steroid hormones is a plausible explanation of the association of oestrogen levels with breast cancer.

13. Before it can affect cells, IGF-I first needs to bind to receptors on the target cell, principally type-1 IGF-receptors (Cullen, *et al*., 1990; McCusker, 1998; Pollak, *et al*., 1992). In biopsy samples, the number of IGF-receptors on the membranes of breast cancer cells was generally greater than on cells taken from patients with benign breast diseases. The total level of circulating IGF-I is generally greater than the amount needed for maximal receptor stimulation (Perks and Holly, 2000), but the activity of circulating IGF-I is reduced by binding to IGF-binding serum proteins, especially IGFBP-1 and IGFBP-3 (Yu and Rohan, 2002). IGF-I activity in tissues is influenced not only by local tissue expression and regulation of IGFs, IGF-binding proteins and IGFBP proteases, but also by factors that influence their circulating concentrations, which in turn can affect the amount of IGF-I delivered to tissues (Perks and Holly, 2000). The activity of IGF-I on cells is controlled by a complex set of factors, including circulating levels of hormones and growth factors such as oestrogens and epidermal growth factor (Yu and Rohan, 2002), local levels of zinc ions (McCusker, 1998) and of 1,25-hydroxyvitamin D (Fonfa, 2002). The book also claimed that vitamins A and D played a role in reducing blood levels of IGF-I, but the reference given (Hunter and Willett, 1993) made no mention of this. The book's claim that vitamin D blocked breast cancer appeared to be based on the results of Fonfa (2002), which showed that 1,25-hydroxyvitamin D could cause increased production of IGFBP-3 by cancer cells *in vitro*.

14. It was claimed in the book that consuming dairy products increases circulating levels of IGF-I, but the references that were given as the source of this information (Butler, 2006; Yakar, *et al*., 2005) made no mention of this. However, it has been shown elsewhere in epidemiological studies that diet can influence the amounts of IGF-I and its binding proteins in serum. High consumption of tomatoes was associated with low levels of serum IGF-I and to a lesser extent a reduced ratio of IGF-I to IGFBP-3 (Mucci, *et al*., 2001). High consumptions of tomato ketchup and tomato juice were associated with a low ratio of IGF-I to IGFBP-3 in serum (Gunnell, *et al*., 2003). Professor Plant's book misquoted Yu and Rohan (2000) to give support to a claim that dietary interventions to reduce levels of active IGF-I could prevent certain cancers. Actually, Yu and Rohan (2000) stated *"Currently unknown are the feasibility and validity of implementing dietary interventions to reduce IGF-I levels with the goal of preventing cancer"*. Nevertheless, it is well recognised that diet can affect cancer risk in laboratory animals and in humans. The book made reference to several reports of effects of diet on IGF-1 levels or cancer risks.

- Allen, *et al*. (2005) found that serum IGF-I levels were similar in 226 meat eaters and 237 vegetarians, but that the levels were 9% lower (statistically significant) in 233 vegans. Total serum testosterone was also raised in vegans, but free testosterone, androsterone glucuronide and luteinising hormone were unaffected.
- Campbell and Campbell (2005) claimed that the consumption of animal-based foods such as meat and milk can cause the body to produce increased

amounts of IGF-I, but they made no reference to any results of experiments that would support this claim.

- A report that was cited by Professor Plant (World Cancer Research Fund, 1997) stated that there is “convincing” evidence that eating vegetables decreases the risk of colorectal cancer. Eating fruit and vegetables “probably” decreased the risk of breast cancer and “possibly” decreased the risk of ovarian cancer. Eating vegetables “possibly” decreased the risk of prostate cancer. The report stated that milk probably protects against colorectal cancer but diets high in calcium are a probable cause of prostate cancer. Various dietary factors also affected the incidences of other types of cancer
- A review article (Yakar, *et al*., 2005), that was cited by Professor Plant in support of her claim that dietary dairy products affected circulating levels of IGF-I, covered the role of IGF-I in tumour growth and progression. It briefly mentioned that energy-restricted diets led to a significant reduction in circulating IGF-I levels and were shown to correlate with decreased cancer incidence in several mouse models. However, no mention was made of any possible effect of dietary dairy products on IGF-I levels.

Professor Plant claimed in the book that risks of some cancers may be mediated by circulating levels of bioactive IGF-I that can be affected by diet, and this claim seems reasonable. However, this does not necessarily mean that dietary levels of IGF-I have any influence on these cancer risks.

15. It was correctly claimed that milk contains IGF-I (Akre, 1989; Epstein, 1990a and 1996). The amino acid sequence of IGF-I is highly conserved in mammalian species and is identical in humans, cattle and pigs (European Commission, 1999). Thus the IGF-I in cows’ milk would be expected to be biologically active in humans. Furthermore about 3% of the IGF-I in milk is in N-terminally truncated forms (missing a few amino acids) that are up to 10 times more potent than normal IGF-I (European Commission, 1999). Treatment of cows with bovine somatotropin (BST) can cause the IGF-I levels in milk to be increased (Mepham, *et al*., 1994), but high yield breeds of cows also produce milk containing relatively high concentrations of IGF-I (Butler, 2006; European Commission, 1999). Milk obtained from pregnant cows also contains high levels of IGF-I (Butler, 2006). Administration of BST to lactating cows caused increased serum levels of IGF-I and the IGF-binding protein, IGFBP3; whereas levels of IGFBP-2 were decreased in serum but increased in lymph (Cohick, *et al*., 1992). It has been reported that milk from BST-treated cows could contain up to 30 ng/mL of IGF-I, whereas bulked milk in the USA contained 1 to 8 ng/mL (Mepham, *et al*., 1995; Outwater, *et al*., 1997). Human milk contains 6 to 17.6 ng/mL (Outwater, *et al*., 1997). Miller, *et al*. (1989) reported that pasteurisation (heating to 175ºC for 45 seconds) did not reduce the concentration of IGF-I in cows’ milk (about 7 ng/mL), whereas more extreme heat treatment (250ºC for 5 minutes) destroyed the IGF-I to give a concentration that was less than 1 ng/mL.

16. Little mention was made of the amounts of IGF-I in foods other than dairy products. The book mentioned that treatment of cattle with growth-promoting hormones increased the levels of IGF-I in meat. However, the reference cited in support of this claim (Simpson, *et al*., 1997) did not mention levels in meat, but noted that mean plasma levels of IGF-I in untreated Brahman and Angus cows were 164.1 and 98.4 ng/mL, respectively. Treatment of the cattle with a growth-promoting sub-cutaneous implant of oestradiol-17β caused the plasma IGF-I in both breeds to

increase to approximately 220 ng/mL. This was accompanied by an increase of 11% in the level of IGF-I binding to plasma proteins.

17. The book points out that circulating levels of IGF-I can be affected by diet:

- Norat, *et al*. (2007) performed a cross-sectional study in 2109 women from various European countries who were controls in a case-control study of breast cancer nested in the European Prospective Investigation into Cancer and Nutrition (EPIC). Diet was estimated through questionnaires and concentrations of IGF-I and IGFBP-3 were measured in serum. The effect of different intakes of various nutrients and food types upon levels of IGF-I and IGFBP-3 were measured by comparing the levels in 1st quintile consumers (low intake) for each food/nutrient with the levels in the 5th quintile (high consumers). Levels of IGF-I were significantly ($p<0.05$) increased with increased intakes of protein, riboflavin, vitamin B6, calcium, magnesium, phosphorus, potassium, milk and cheese; whereas IGF-I decreased with increased intakes of polyunsaturated fat, beta-carotene and vegetables. For IGFBP-3, levels increased with higher intakes of phosphorus and cheese and decreased with calcium and processed meat. The strongest associations (<0.001) were for the increases in serum IGF-I with increased consumptions of protein, calcium and phosphorus. *[The secretariat notes that a recent epidemiological study of 36,965 male and 16,605 female cancer cases showed decreased risk of cancer, especially colorectal cancer, in those with high intakes of dairy products and calcium (Park, et al., 2009).]* The authors of the study (Norat, *et al*., 2007) commented that they could not estimate the intake of protein by source, because this information had not been standardised across centres in EPIC. However, they noted that mean serum concentrations of IGF-I increased with increasing levels of consumption of red meat ($p=0.27$), poultry ($p=0.18$), fish ($p=0.84$) and eggs ($p=0.56$), all sources of animal protein, but none of the relationships were statistically significant.
- Rose, *et al*. (1986) compared 1978-1979 mortality rates for cancers of the breast, prostate, ovary and colon in 26-30 countries with the average 1979-1981 food availability data published by the United Nations. Ovarian cancer was positively associated with milk intake and negatively associated with cereal intake.
- In a study of 204 healthy men and women in the USA (Heaney, *et al*., 1999), people having 3 servings per day of low fat milk had a 10% increase in serum IGF-I and a 1.9% decrease in serum IGFBP-4 (controls had a 7.9% increase in IGFBP-4 in the same period).

Professor Plant's book stated that there were a few studies that showed that consumption of dairy products caused decreases in IGF-I levels or caused decreased prevalences of various types of cancer, and added that the validity of such results had been questioned. However, it provided no references to these studies or to those who had questioned the results.

18. The book claimed that, although IGF-I is essential for growth, its levels do not correlate closely with growth rates and that this suggested that circulating IGF-I levels reflect nutritional status. This claim was not supported by the information given in the two articles that were cited. Underwood, *et al*. (1980) reported that measurement of serum IGF-I was useful for evaluating patients with acromegaly but

less useful for those with growth failure due to hypopituitarism. Perdue (1984) noted that elevated levels of IGF-I positively correlated with skeletal growth in adolescents.

19. Reference is made in the book to several studies that it claims showed an association between blood levels of IGF-I and increased risks of certain cancers, including cancers of the breast, ovary, prostate, lower bowel and lung (Holly, 1998; Yu and Rohan, 2002). Most of the references were to studies that investigated the effects of diet on cancer incidences, but that did not actually mention circulating levels of IGF-I. However, a few of the studies did investigate the association between IGF-I levels and cancer risks.

- In relation to breast cancer, higher levels of plasma IGF-I were found in female breast cancer patients than in controls of similar ages (Peyrat, *et al*., 1993). In a nested case-control study conducted within the Nurses' Health Study cohort (Hankinson, *et al*., 1998), concentrations of IGF-I and IGFBP-3 were measured in prospectively collected plasma samples. The plasma IGF-I results for 397 women who were diagnosed with breast cancer in the 4 to 5 years following the blood collection were compared with those for 620 age-matched controls. There was an increased risk of breast cancer (relative risk = 2.88) in pre-menopausal women with a high plasma level of IGF-I (>207 ng/mL), but not in post-menopausal women (RR = 0.85). The risk was particularly high (RR = 7.28) in pre-menopausal women older than 50 years of age. An association between high plasma levels of IGF-I and risk of breast cancer was also seen in a case-control study (Bruning, *et al*., 1995) and a small clinical study (Peyrat, *et al*., 1993), but the designs of these two studies were such that it was not possible to look into whether there was a temporal relationship.
- For ovarian cancer risk, reference was made to Rose, *et al*. (1986), which noted a positive association between ovarian cancer mortality and milk intake but did make any mention of IGF-I levels.
- In relation to risk of prostate cancer, a nested case-control study within the Physicians' Health Study cohort had been conducted on prospectively collected plasma from 152 prostate cancer cases and 152 control subjects, and it was found men in the highest quartile of plasma IGF-I levels (293.76 ng/mL or more) had a relative risk of 4.3 compared to men in the lowest quartile (184.8 ng/mL or less) (Chan, *et al*., 1998).
  Harman, *et al*., (2000) reported the findings of a prospective cohort, case-control study which showed high plasma IGF-I to be associated with increased prostate cancer risk, with an odds ratio of 3.1.
  Stattin, *et al*. (2000) reported the results of a nested case-control study men with elevated plasma levels of IGF-I may have an increased risk of prostate cancer. Men who developed prostate cancer 1 month to 10 years after blood collection were found to have had statistically significantly higher concentrations of IGF-I than cancer-free control men. The association was particularly strong in younger men.
  Chokkalingam, *et al* (2001) performed a case-control study in a Chinese population that had a low risk of prostate cancer. Men in the highest quartile for the IGF-I:IGFBP-3 molar ratio (an indirect measure of free IGF-I) had a 2.5-fold higher risk compared with those in the lowest quartile (odds ratio = 2.51).
  Mantzoros, *et al*. (1997) took blood from prostate cancer patients and from patients with benign prostatic hyperplasia then compared IGF-I levels with

blood from healthy controls. Mean concentrations of IGF-I were higher in both sets of patients than in controls but the increase was greater and was statistically significant only in the prostate cancer patients.
Wolk, *et al.* (1998) performed analyses of levels of IGF-I and IGFBP-3 in blood from newly diagnosed prostate cancer patients as part of a Swedish case-control study. Serum IGF-I was statistically significantly higher in prostate cancer patients than in control subjects, with the difference being greatest in those younger than 70-years-of-age. No association was found between serum IGF-I levels and disease stage. There was no significant difference between prostate cancer patients and controls with regard to IGFBP-3 levels.

- For colorectal cancer, a nested case-control study within the Physicians' Health Study cohort had been conducted using prospectively collected plasma from 193 men who had developed colorectal cancer in the following 13 years and 318 age- and smoking-matched control men (Ma, *et al*., 2001). The risk of colorectal cancer was compared with dietary factors and with plasma levels of IGF-I and IGFBP-3. Intakes of skimmed milk, low fat milk, calcium from milk and calcium from dairy produce were associated with modest increases in plasma IGF-I, but intakes of red meat, poultry and fish were not associated with plasma IGF-I levels. Non-drinkers of milk who had the highest tertile ratio of IGF-I to IGFBP-3 had an increased risk of colorectal cancer (relative risk = 3.05) but no significant increased risk was seen in frequent drinkers of low fat milk with the highest tertile ratio of IGF-I to IGFBP-3 (relative risk = 1.05).
- With reference to lung cancer risk, Yu, *et al*. (1999) looked at blood levels of IGF-I, IGF-II and IGFBP-3 in newly diagnosed lung cancer patients and control subjects. They found elevated IGF-I and reduced IGFBP-3 in lung cancer patients. The risk of lung cancer in subjects having upper quartile levels of IGF-I had an odds ratio of 2.06.

It was assumed in the book that elevated blood levels of IGF-I caused the cancers (as opposed to the other possibility that cancers could cause IGF-I to be elevated).

20. It was claimed in the book that a European scientific committee concluded that excess levels of IGF-I in milk form cows treated with BST pose a serious risk of breast or prostate cancer in consumers. The conclusions of the Scientific Committee on Veterinary Measures Relating to Public Health were:

- Direct risks associated with the use of rBST in dairy cows appear to be related to the possible increase of IGF-I levels in milk. The diverse biological effects attributable to the intrinsic activity of IGF-I, exerting a broad variety of metabolic responses through endocrine, paracrine and autocrine mechanisms, make the definition of an *in vivo* quantitative dose-effect relationship virtually impossible.
- Risk characterisation has pointed to an association between circulating IGF-I levels and an increased relative risk of breast and prostate cancer. In addition, the possible contribution of lifespan exposure towards dietary IGF-I and related proteins present in milk from rBST-treated cows, to gut pathophysiology particularly of infants, and to gut associated cancers need to be evaluated.
- The available data basis for exposure assessment, ie. the amount of IGF-I and/or its truncated forms excreted in milk following the administration of rBST to dairy cows is incomplete.

Thus the conclusions of the EC committee were less dogmatic than was suggested in the book, with recommendations being made for further work to clarify outstanding issues. Furthermore, the UK's Veterinary Products Committee (VPC, 1999) concluded that ingesting milk from rBST-treated cows would not be likely to add to the risk of developing cancers of the breast or prostate.

21. The book also misquoted a report (Council on Scientific Affairs, American Medical Association, 1991) of discussions of the American National Institutes for Health (NIH). It claimed that, whilst the NIH had concluded that use of BST in cows was safe, it had recommended that *"Further studies will be required to determine whether ingestion of … bovine IGF-I is safe for children, adolescents and adults"* and it acknowledged that *"Whether the additional amount of insulin-like growth factor in milk from [rBST-treated cows] has a local effect on the oesophagus, stomach or intestines is unknown."* The first quote was incompletely reported; the full quote is *"Further studies will be required to determine whether ingestion of* ***higher than normal concentrations of*** *bovine IGF-I is safe for children, adolescents and adults."* The second quote was not given in the article that had been cited (Council on Scientific Affairs, American Medical Association, 1991).

22. Support for the hypothesis that high circulating levels of active IGF-I can increase the risk of some cancers was given by the observation of a high prevalence of colorectal neoplasia in people with acromegaly, who have high levels of endogenous production of growth hormone and IGF-I (VPC, 1999). Further evidence in support of the hypothesis is given by the observation that use of tamoxifen against breast cancer reduced serum concentrations of IGF-I (Pollak, *et al.,* 1992). Pollak, *et al*., (1992) hypothesised that blockade of oestrogen receptors in the hypothalamic-pituitary axis by tamoxifen could inhibit the release of growth hormone, which in turn could lead to reduced hepatic production of IGF-I. It was also proposed that some oncogenes might act by causing increased production of growth factors (eg. IGF-I) or their receptors on cell membranes (eg. type 1 IGF-receptor), resulting in increased cell proliferation (Heldrin and Westermark, 1984), but no experimental evidence was present in support of this hypothesis.

23. Cells of the body could potentially be exposed to dietary IGF-I either directly or systemically following absorption from the gut.

- Cells lining the gut could be exposed to any IGF-I that survives the digestion process. The book claimed that IGF-I is resistant to digestion by gastrointestinal enzymes, but this claim was not entirely in line with the results of the results reported in the articles that were cited. There is evidence that, in neonates, some dietary IGF-I reaches the gut lining in biologically active form, and it is feasible that the IGF-I in colostrum might play an important role in the growth and differentiation of the neonate gut (European Commission, 1999). Oral doses of IGF-I remained receptor-active in gastrointestinal tissues of suckling rats for at least 30 minutes post-ingestion (Philipps, *et al*., 1995). Feeding infant rats with IGF-I increased the migration of enterocytes from crypts in the small intestine (Philipps, *et al*., 1997). Oral doses of 1 µg IGF-I/animal/day for 6 days stimulated brush border enzymes in rat pups (Burton, *et al*., 1994). IGF-I was more readily digested by gastrointestinal juices in adults than in neonates: Rao, *et al.* (1998) found degradation in luminal flushings from the duodenum, jejunum, mid-jejumum and ileum of adult rats

was several times greater (3.3 to 35 times, depending on the region) than in 12-day-old rats. In adult rats, there was rapid proteolysis of IGF-I by digestive juices (Xian, *et al*., 1995, measured degradation half-lives of 2-8, 2, 2 and 16-38 minutes *in vivo* in ligated gut segments of stomach, duodenum, ileum and colon, respectively). In contrast, Rao, *et al*., (1998) reported that no breakdown of IGF-I occurred in flushings from the stomachs of adult rats. Dietary components may protect IGF-I from digestion. *In vitro* studies with fluids from the stomach and jejunum showed that acidic proteins, such as casein and bovine serum albumin, protected IGF-I from proteolysis (Xian, *et al*., 1995). When the Veterinary Products Committee (VPC) assessed the safety of use of BST in cows, it could not exclude the possibility that IGF-I in ingested milk might reach the cells lining the gut and cause increased risk of colorectal cancer in consumers (VPC, 1999).

- Dietary IGF-I can only affect other tissues of the body if it is absorbed from the gut. There is evidence that some absorption of active IGF-I might occur in young animals. Oral doses of IGF-I given to suckling rats caused increased bodyweight gain and increased the weights of some organs (Philipps, *et al*., 1995). The VPC considered it unlikely that sufficient active IGF-I from the diet could be absorbed to increase the amount of circulating IGF-I sufficiently to have any effect on tissues (VPC, 1999), as the normal concentration of endogenous IGF-I in the blood was much greater than the concentration that could occur in the gut lumen as a result of drinking milk.

Overview of the Main Conclusions of the Book as they Relate to IGF-I

24. It was claimed in the book that that the evidence of an association between dietary exposure to IGF-I and cancer incidence is consistent with several of the criteria for causality that were proposed by Bradford-Hill (1965). The variables proposed by Bradford-Hill were: strength, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment and analogy. There was reasonably good evidence to indicate that elevated circulating levels of IGF-I were associated with an increased incidence of cancer. However, it was not clear from the evidence presented in the book whether eating foods containing relatively high levels of IGF-I could cause an increased risk of any type(s) of cancer. Furthermore, it is hard to envisage a mechanism whereby dietary IGF-I would be absorbed from the gut in a biologically active form and in sufficient quantities to cause a biologically significant increase in the amount of circulating free IGF-I to cause any effect on breast or other systemically exposed tissues. Note that blood levels of free IGF-I are normally higher than the levels found in milk and that IGF-I is a polypeptide that would be expected to be subject to normal digestive processes in the gut (although some protection might be given by casein and other dietary proteins).

25. It is also unclear whether the diet promoted by Professor Plant, The Plant Programme, has any effect on the risk of developing cancer or any effect on those with existing cancer. The case studies given in the book give some anecdotal support for The Plant Programme, but no impartial observations of people following this diet have been presented. As explained in Chapter 3 of the book, Professor Plant recognised that there was a lower prevalence of breast cancer in women in China than in women in the Western world, and she considered it likely that the main factor affecting this difference was diet. The Chinese tend to eat fewer calories, less fat and

no dairy products. The Plant Programme is based around the Chinese diet, with an emphasis on omitting dairy produce from the diet. The fact that milk and dairy products contain IGF-I was presented as one reason why the Plant Programme should reduce cancer risk, but the evidence given for this was incomplete, and there may be other reasons why breast cancer is less common in China than in the West. No information was given on dietary sources of IGF-I other than milk, so it was not clear whether milk is a major source of dietary IGF-I.

Conclusions

26. In commenting on the issues raised by Professor Plant's book "Your Life In Your Hands", the Committee may wish to consider the following conclusions:

1) The book presented evidence on the role of IGF-I in cell proliferation and cancer in support of a claim that risks of certain cancers, particularly breast and prostate cancers, are increased by consumption of dairy products and that the increased risk is a result of the presence of IGF-I in milk. The evidence presented was incomplete, and of inconsistent quality, so any conclusions drawn from the book must be regarded as provisional and would need to be confirmed following a fuller systematic search of the scientific literature before they could be acted upon.

2) The book identified that IGF-I has a role to play in the normal growth and development of tissues, and that locally high levels of IGF-I or increased sensitivity to IGF-I can also cause cancer cells to multiply. Thus IGF-I is one of the many substances that have been shown to play a role determining the growth and development of cancers.

3) The book did not provide convincing evidence to justify the claim that the IGF-I in milk and dairy products (or in any other food) could cause consumers to have increased risks of developing certain cancers.

4) Although it is recognised that cancer risks can be affected by dietary interventions, the book provided insufficient evidence to demonstrate unequivocally that people following The Plant Programme would have a lower risk of any type of cancer.

5) Information was provided on the amount of IGF-I in milk, but nothing was presented on the amounts of IGF-I in other foods.

6) There is a potential for dietary IGF-I to come in contact with the cells lining the gastrointestinal tract. However, no information was presented on the concentrations of IGF-I that these cells could be in contact with.

7) No information was presented on the amount of breakdown of IGF-I that might occur in the gut lumen, although there was some evidence that casein and some other dietary proteins might give some protection from breakdown and there was evidence that partial breakdown to N-terminally truncated forms could increase the potency of IGF-I.

8) No information was presented on the amount of IGF-I from dietary sources that might be absorbed from the gut lumen into the bloodstream.

9) There was evidence (in the book?) that showed that IGF-I could cause mitosis and apoptosis to occur *in vitro* in some cell lines, including several derived from cancer cells. It was also claimed that IGF-I caused differentiation of cells, but the references that were cited presented no evidence from experiments in support of the claim.

10) The book presented evidence that showed an association between blood levels of free IGF-I and risks of some cancers. However, it was not clear whether the cancers were caused by the high IGF-I or whether the high IGF-I was a consequence of the cancers.

Recommendations

26. Members are asked to advise on whether further investigation of the possible cancer risk from dietary IGF-I can be justified. Although Professor Plant's book does not provide sufficient evidence to demonstrate convincingly that high levels of dietary IGF-I can cause increased risk of cancer, the Committee might wish to advise the Secretariat on lines of enquiry that could be pursued should interested parties (eg. the Food Standards Agency or the Veterinary Medicines Directorate) wish to investigate the possible consequences of eating foods that might contain IGF-I. The Secretariat could perform searches of the scientific literature to investigate in a more balanced and systematic way:

- The concentrations of IGF-I in various foods.
- Whether eating foods high in IGF-I was associated with any types of cancer.
- The fate of IGF-I in the gut lumen.
- The amount of absorption of IGF-I and its biologically active truncated forms.
- Whether cancer can be caused as a result of direct exposure of the cells lining the gut to IGF-I in the gut lumen.

Are there any other lines of enquiry that could be considered?

Secretariat
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