rBST (NUTRILAC) "GAPS ANALYSIS" REPORT
By
rBST INTERNAL REVIEW TEAM

Health Protection Branch, Health Canada

April 21, 1998

Team Members:

- Shiv Chopra, B.V. Sc., M.Sc., Ph.D.
  - Human Safety Division
  - Bureau of Veterinary Drugs
  - Food Directorate

- Mark Feeley, B.Sc., M.Sc.
  - Chemical Health Hazard Assessment Division
  - Bureau of Chemical Safety
  - Food Directorate

- Gerard Lambert, D.M.V., M.Sc., Ph.D.
  - Human Safety Division
  - Bureau of Veterinary Drugs
  - Food Directorate

- Then Mueller, B.Sc., Ph.D.
  - Office of Science
  - Therapeutic Products Directorate

Coordinator (rBST File Manager):

- Ian Alexander, D.V.M.,M.Sc., Ph.D.
  - Pharmaceutical Assessment Division
  - Bureau of Veterinary Drugs
  - Food Directorate

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V1. Monsanto study on Immunoglobulin in Rat Serum

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Executive Summary

Nutrilac, a genetically engineered bovine growth hormone (BGH), technically called recombinant bovine somatotropin (rBST), is a uniquely controversial veterinary product throughout the world. Approved by US FDA but not yet approved by Health Canada and several other national regulatory agencies, it is claimed to increase the average milk yield in dairy cows by 10-15 percent.

The reason for this report is to determine whether the required human safety review and evaluation for this drug were adequately addressed and, if not, to provide a critical "gaps analysis" of same.

Both procedural and data gaps were found which fail to properly address the human safety requirements of this drug under the Food and Drugs Act and Regulations.

The question of the oral absorption of rBST and IGF-1 was not adequately addressed. Specifically:

> Evidence from the subchronic rat study submitted by Monsanto had shown that rBST was absorbed intact from the GI tract following oral administration, albeit at high doses, and elicited a primary antigenic response (IgG antibodies). The full immunological and potentially toxicological consequences of this observation were not investigated.
>
> IGF-1 also can survive the GI tract environment to produce local effects. Under exposure conditions, which would mimic the human scenario (i.e., in milk), IGF-1 appears also to be absorbed intact from the GI tract. The full significance of this finding also was not investigated.

In addition, based on the proposed label supplied by Monsanto, the increased risk of mastitis that may be associated with the use of rBST (Nutrilac) has human health implications (antibiotic resistance in farm-borne human pathogens).

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Preamble

Before any veterinary drug can be marketed in Canada, the Food and Drugs Act and Regulations require that the manufacturer submit scientific data demonstrating that the drug is safe and effective when used in accordance with the directions on the label. The specific unit that is mandated to implement this part of the Food and Drugs Act and Regulations at Health Canada is the Bureau of Veterinary Drugs (BVD) in the Food Directorate of Health Protection Branch. Within BVD the unit that conducts the human safety evaluation of all veterinary drugs for food producing animals is the Human Safety Division (HSD).

NUTRILAC, a "recombinant" Bovine Somatotropin (rBST) from Monsanto Canada, is one of several copies of the naturally occurring bovine growth hormone (BGH), produced by "genetic engineering". Each of these products is designed for commercial application in dairy cows with claims to increase their average milk production by "10-15 percent".

Historically, Canadian submissions for four different rBST products at BVD trace back to approximately fifteen years. These pertain to applications for Experimental Studies Certificate, Investigational or New Drug submissions. However, all of these products have a history of being mired with intensely conflicting scientific opinions about their safety to both cows and humans. Concerning human safety, there are scientists who opine that being chemically similar to the endogenously produced BST, regardless from which manufacturer, each and every rBST should be subjected to all the prevailing and perhaps even more stringent requirements of the Canadian Food and Drugs Act and Regulations. In contrast, there are those who argue that because rBST (rBGH) is a virtual copy of the natural BST (BGH) even the regularly required human safety tests are not necessary. According to the latter opinion, the tests that should not be required, are particularly those which call for a thorough long-term toxicology evaluation for human safety, due especially to such possibilities and potential as genetic sterility, infertility, birth defects, cancer and immunological derangement(s).

The only rBST Submission which is currently being considered in Canada is for Nutrilac by Monsanto Canada. A second submission on a product called Somidobove (Optiflex) was stayed at the request of its manufacturer, Elanco Canada, pending the outcome on Monsanto's Nutrilac. All the other submissions from potentially additional manufacturers of rBST have allegedly been withdrawn. Among these manufacturers included such names as Provel, American Cyanamid, and Coopers Agropharm.

The New Drug Submission on Nutrilac has been at BVD since February 19, 1990. Records indicate that the manufacturer of this product did not subject it to any of the normally required long-term toxicology experimentation and tests for human safety. Nor, at any time, did the Chief of Human Safety Division, Dr. M.S. Yong, appear to have asked for these tests from this or any other manufacturer of rBST submissions. That no such tests should be necessary was due apparently to a mutually agreed upon assumption between Health Canada and the manufacturers of rBST products. Hence, the conflict; and the present, "gaps analysis", review by the rBST Internal Review Team.

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The Team

Appointed on January 2, 1998, the proposal to establish the rBST Internal Review Team on Nutrilac was due specifically to resolve a much prolonged issue at the Bureau of Veterinary Drugs in that, except for certain managers, the other relevant staff consistently complained that the conclusions and recommendations to state that rBST treatment of dairy cows "posed no human health risk" may not be based on critically sound scientific considerations as required under the Food and Drugs Act and Regulations. They also complained that the management policy to grant a special confidentiality to only the rBST files and reviews, away from the relevant staff, was wrong. They requested that, given the highly controversial history of this product in the public domain, a more thorough examination should be ordered.

Prior to the appointment of the Team two of its members, Dr. Shiv Chopra and Dr. Gerard Lambert, who are long-time employees in the Human Safety Division had volunteered to examine all the various rBST-related human safety reviews and opinions on BVD files and thus produce a jointly coordinated "gaps analysis" for Dr. George Paterson who is Director General, Food Directorate, and the Chair of Health Canada rBST Advisory Committee. In reference to this exercise it was generally agreed to consult with the entire

membership of Human Safety Division, including Dr. Yong. The projected time-frame to complete this exercise was indicated to be toward the end of February 1998.

However, this work was not yet begun when Dr. Paterson decided to appoint the present, more diverse, Team; with a somewhat different and considerably more expanded task. The task which the Team received from Dr. Paterson was to jointly examine all available reviews and commentaries on Nutrilac rBST at BVD and thereby produce a "gaps analysis" report which, in turn, would be forwarded to two additional, "External Review", committees, with members obtained from the Royal College of Physicians and Surgeons and the Canadian Veterinary Medical Association. (For history of Team see Appendix 1).

Dr. Thea Mueller, presently on secondment to the Office of Science from the Bureau of Pharmaceutical Assessment, has 17 years experience in the pre-market safety and efficacy evaluation of drugs for human use.

Mr. Mark Feeley, from Toxicology Evaluation Section of the Bureau of Chemical Safety, is involved in the risk assessment of all food-borne chemicals.

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Team Members

- Dr. Ian Alexander: Coordinator
  - Pharmaceutical Assessment Division
  - Bureau of Veterinary Drugs
  - Food Directorate

The role of the Coordinator was limited strictly to provide data and other facilities to the Team and not to be personally involved in the actual review and deliberations.

- Dr. Shiv Chopra, Member
  - Human Safety Division
  - Bureau of Veterinary Drugs
  - Food Directorate

- Dr. Gerard Lambert, Member
  - Human Safety Division
  - Bureau of Veterinary Drugs
  - Food Directorate

- Mr. Mark Feeley, Member
  - Chemical Health Hazards Assessment Division
  - Bureau of Chemical Safety,
  - Food Directorate

- Dr. Thea Mueller, Member
  - Office of Science,
  - Therapeutic Products Directorate (human)

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Role of the Team

> "Review the data comprising the human safety data package for the Nutrilac (rBST) new drug submission, in particular items 1, 2, 4, 7, 8 and 9 (see below for list of Data Package for Team Review).
>
> Determine if any gaps exist in the scientific data regarding the human health risks associated with the Nutrilac (rBST) in Canadian dairy cattle."

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Data Package For Team Review

Team Coordinator (rBST File Manager), Dr. Ian Alexander, -provided each Member with a data package containing the following items:

1. Human Safety Report by D.R. Casorso, 1990 (Nutrilac File).
2. Human Safety Report by M.S. Yong, 1995 (Nutrilac File).
3. Human Safety Reports by M.S. Yong, General rBST and IGF-1 Reports, 1995 (General Report File)
4. Human Safety Report, Antigenicity of bst, M.S. Yong, 1998 (General Report File).
5. Human Safety Report, Need for Chronic Toxicity, M.S. Yong, 1998 (General Report File).
6. U.S. FDA Freedom of Information Summary Posilac, 1993.
7. Science Article, 1990, FDA Human Safety Evaluation
8. U.S. National Institutes of Health Report on Human Safety, JAMA, 1991.
9. U.S. National Institute of Health Statement on rBST, 1990.
10. European Commission Scientific Conference on Growth Promotion, 1995.
11. European Commission Evaluation Report on rBST, 1993
12. JECFA Evaluation Summary, 1993.
13. WHO Toxicology Review, 1993.
14. FAO Residue Report, 1992.
15. FDA responses to concerns expressed by Dr. Epstein.
16. FDA responses to concerns expressed by Ms Mullarkey.
17. FDA responses to concerns expressed by Mr. J. Rifkin.
18. FDA responses to concerns expressed by Mr. J. Rifkin.
19. FDA responses to concerns expressed by Mr. J. Rifkin.
20. FDA responses to concerns expressed by Johanna Dairies.
21. List of references and copies of major references.
22. Toronto Food Policy Group Position Paper.

NOTE: During the course of Team deliberations, several additional reports, opinions and correspondence were needed. The most pertinent of these reports and correspondence included a copy of the latest (1997) submission by Monsanto to JECFA and the numerously exchanged commentaries between the objectors of rBST and certain Health Canada officials.

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Team Concerns and Issues

Data Package

Right at the outset the Team recognized that, so far, the only major country allowing the sale of a commercially prepared rBST for milk enhancement was in the USA. However, even in that country where a single such product, Posilac (Nutrilac), was approved it was attached to an intricately involved epidemiological field surveillance of the future animal safety by the manufacturer. In contrast, Canada, Australia, New Zealand and none of the European Union countries had as yet allowed any rBST product to enter in their respective markets.

The listed data package on which the Team was asked to build the required "gaps analysis" was considered to be insufficient. For example, the accompanying rBST submission(s) files and other relevant information were not provided. In contrast, the particular Human Safety Division reviews that the Team was asked to utilize for the "gaps analysis" were found to be extremely scant and sketchy, in that all of them appeared to be based on information that comprised of review articles or summaries of data that the manufacturer supplied. Moreover, the usually required review procedures, applying to all other new drug submissions, did not appear to be followed for any rBST submission.

There was also the question of a ready referral to the original or confirmatory reports on the various adverse effects in rBST-treated cows in U.S., such as undue tissue-growth, birth defects, increased incidence of mastitis and the relevant mastitis-induced antibiotic resistance, which the Team could utilize to clue into a direct or indirect long-term safety hazard of this product to humans.

Consequently, the Coordinator, Dr. Ian Alexander, was asked to make the following provisions:

1. To procure copies of the duly referenced publications, particularly in the evaluation reports of Dr. M.S. Yong.

2. To produce BVD files on all rBST-product(s).

3. To locate all data volumes on Nutrilac Submission'.

4. To provide file(s) and review(s) on any other types of related somatotropin products, e.g. rPST for pork production.

5. To arrange short personal meetings for the Team with key evaluators (previous, present, special advisors etc.) on all somatotropin submissions at BVD. In particular, the following individuals were identified:

   Dr. Ian Alexander as the current BVD evaluator of all rBST-related animal safety data, since 1994.
   Dr. Margaret Haydon, as the previous BVD evaluator of same, up to 1994.
   Dr. Sudarshan Malik as a generally recognized BVD advisor on mastitis.
   Dr. Cris Basudde and Dr. Gerard Lambert as the two human safety evaluators of a porcine somatotropin submission at BVD.

6. To locate and provide any other relevant information on rBST, including private reviews, commentaries, correspondence, particularly with Dr. M.S. Yong.

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Team Records

Given the public controversy around Nutrilac submission it was important for the Team to maintain a most thorough and diligent record for both its oral and written deliberations. The simplest and the most efficient method that the Team adopted was to tape-record all the oral deliberations. However, to ensure their confidentiality, the sole custodian of all the ensuing tapes was agreed to be rBST File Manager, Dr. Ian Alexander.

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Team Methodology

In addition to the initially received documents, all Members of the Team were allowed a complete and uninhibited access to all the rBST files and data at BVD. However, given the size of the task at hand and the urgent stipulations of time by the Chair, BVD rBST Advisory Committee, Dr. George Paterson, the total Team work was categorized into separate undertakings and then each individual Member was asked to provide a lead role toward a speedy completion. Who did what was decided by a common agreement and convenience of the whole Team. The various individual roles that Members provided were as follows:

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Individual Responsibilities of Team Members

Dr. Ian Alexander
General arrangements to: provide the necessary data, files and other relevant information on Nutrilac and any other rBST submissions at BVD; act as conduit between Team Members and Dr. Paterson on the rBST Advisory Committee policy and procedures; and safe-keep all Team meeting records on tape.

Dr. Gerard Lambert
Meeting agendas, between meeting communications with Team Coordinator, procurement of selective raw data on Nutrilac.

Dr. Thea Mueller and Mr. Mark Feeley
Chronological review and report on all rBST files at BVD.

Dr. Shiv Chopra
Compilation of sectional drafts and final report.

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Team Findings

Information Gaps in BVD Review Process

Monsanto Files

Experimental Studies Certificate (ESQ File No. 9459-MO298-3

May 25, 1988: ESC issued to E. Block, McGill, despite deficiencies in information: Data submitted in support of the application involved a form of BST different from what was intended to be used in the study (injectable zinc complex vs lyophilized pellets for sc *implantation). Hence,* safety in target species and efficacy data were deemed unsatisfactory. However, a note to file by D.R. Casorso dated May 17, 1988 (ESC filed April 19, 1988) states that there is no risk to human health and that milk from treated cows may be used for food.

November 25, 1988: ESC recommended for U. of Manitoba for prolonged release somatotropin implants (oil suspension). ESC issued despite concerns regarding adequacy of the data and safety in target animal. However, HSD had no objection to allow meat and milk from treated cows for human consumption. Note to file from D.R. Casorso dated December 4, 1988 (ESC filed November 14, 1988) stated that the manufacturer had "submitted substantial data indicating that the consumption of meat or milk from animals treated with sometribove represents no hazard to human consumers". The nature of the data or the reasons why such a conclusion was reached were not described.

January 10, 1989: Same scenario as above with respect to the ESC filed November 16, 1988, by the Livestock Sciences Section, Research Station, Lethbridge, Alberta. Memo from HSD signed by D.R. Casorso. Product was an oil *suspension for* prolonged release.

May 31, 1989: Memo by M.S. Yong, Chief, HSD - no objection to ESC filed by Animal Research Centre, Ottawa, Ontario

May 18, 1989: since any cows treated with BST will not be shipped for human *consumption. Product* was the lyophilized powder of the zinc salt of sometribove in vials.

June 25, 1990: No objection to ESC for use of BST in salmon since none of the treated fish will be made available for human consumption.

October 10, 1990: ESC from U of Guelph states zero withdrawal prior to slaughter.

September 3, 1992: ESC for use of BST in salmon issued provided that the fish are not used as human food.

October 15, 1993: ESC for use of BST in field trial in Atlantic salmon granted provided all fish are destroyed.

Comments:

As early as May, 1988, HSD has gone on record that the meat and milk from BST-treated cows, regardless of its pharmaceutical form, is safe for human consumption. Neither the nature of the data submitted in support of human safety nor the reasons for arriving at the conclusion that there are no safety concerns in humans were ever described. On the other hand, BST-treated fish were always deemed to be unfit for human consumption and bad to be destroyed as a condition of the issuance of an ESC. However, relative rBST for cows no rationale was provided for this apparent discrepancy.

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New Drug Submission #no. 9460-MO298-100, volume 1-10

Sometribove zinc complex (LATECH) - filed February 19, 1990

Data package consisted of toxicity studies in mice, rats and rabbits (2 acute oral studies in rats, I sub-chronic study in mice, 2 acute dermal studies in rabbits, 2 primary irritation studies in rabbits), 3 pharmacokinetic studies in cows, method validation for residue assays, food safety studies to support a zero meat and milk withdrawal (residue depletion studies, BST and antibodies in milk of treated cows, IGF-I levels in milk and plasma of treated cows, IGF-I levels in bulk tank samples, effect of processing on IGFI levels in milk, IGF- I and rBST levels in milk, blood, muscle and liver), intended species safety studies and efficacy studies.

This 40 volume submission was reviewed by HSD in less than two weeks.

March 1, 1990: A brief, 4-page, review by R. Casorso states that there is "no hazard to man consuming milk or meat from sometribove treated animals. No withdrawal period is required." This report did not include an analysis and consequences of the potential oral absorption of rBST as indicated in the immunological study.

March 12, 1990: Letter from M.S. Yong, Chief, HSD, to Monsanto stating that the human safety data are acceptable. This position is maintained throughout the life of the submission, despite concerns from the CNS/Endocrine/Antiparasitic Division.

July 6, 1990 to present: Submission incomplete with respect to safety in intended species and efficacy. Evidence demonstrating safety in target species and efficacy considered inadequate. Concerns over flawed experimental design resulted in a lack of confidence in the entire data package.

August 2, 1990: Manufacturer admits to shortage of Canadian data *and offers to invest in animal research in Canada in exchange for conducting no further experiments and obtaining a NOC on the basis of studies available.

December 18, 1990: Name changed to NUTRILAC. No additional human safety data submitted.

February 2, 1995: Notice of Compliance (NOC) refused on the of basis inadequate evidence

demonstrating efficacy and safety in target animal species.

April 21, 1995: HSD report by M.S. Yong concluding that milk and related products from dairy cows treated with Nutrilac are safe for human consumption with no withdrawal period required.

This report was the first detailed review of the subject especially to discuss IGF-I; safety concerns had never been expressed by HSD ever since 1988. However, it was put on file only in May 1997.

August 24 & September 8, 1995: NOC again refused - risk outweighs benefit. Main issues: serious adverse effects in target animal (reproductive problems, possible teratogenic effects, increased mastitis and lameness, severe reactions to injection sites), failure to show increased milk production under recommended conditions of use by a farmer who would use only approved drugs (studies submitted may have involved the use of unapproved drugs or off-label use of approved drugs), flawed experimental design questions the credibility of the whole data set.

September 14, 1995: Memo to ADM from DG reiterates that there are no human safety concerns. Executive summary covering the period February 1990 to May 1996 repeats the same.

Comments:

There was no critical analysis of the nature of the evidence upon which this conclusion was based, nor was the evidence described in sufficient detail to determine whether such a conclusion is valid. There was no discussion of the consequences of exposure to potentially elevated levels of IGF-I, a polypeptide that mediates many of the physiological actions of BST. The reviewer (Casorso) accepted the manufacturer's contention that sometribove does not cause cancer in man or animals without providing a rationale nor was any explanation given as to why chronic toxicity, carcinogenicity or reproduction/teratogenicity studies were not necessary. There was no discussion on possible antigenicity or other immunological effects nor of potential deleterious effects on the neonate, the subpopulation at greatest risk.

In November of 1993, the FDA approved rBST zinc suspension to enhance milk production in lactating dairy cows, declaring that the milk from treated cows is safe for human consumption. The United States is the only developed country permitting the use of BST, of which there are four manufacturers. There are reports on file that Monsanto pursued aggressive marketing tactics, compensated farmers whose veterinary bills escalated due to increased side effects associated with the use of rBST, and covered up negative trial results. All the four US manufacturers refused to disclose the lists of their research grants to US universities.

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Elanco/Eli Lilly Files File No. 9460-LOO13-513

Somidobove Injection (Optiflex) 320 mg filed March 21, 1988 - 12 "books"

- Book 1
  - C & M- comprehensive summary

- Book 2
  - Animal Toxicology Studies- comprehensive summary
  - 4 studies comprising acute oral and dermal toxicity and primary irritation studies

- 3 dermal sensitization studies
- I 90-day sub-chronic oral study in rats

- Book 3
  - Pharmacology and Residue studies - comprehensive summary

- Book 4
  - Intended species safety studies

- Book 5 & 6
  - Efficacy studies

- Book 7
  - 90 day sub-chronic toxicity study

- Book 8 & 9
  - interim report - chronic toxicity study in cows for 2 lactations

- Book 10, 11 & 12
  - Effect on lactation performance

July 18, 1988: Four months after the submission date (compared to two weeks after the Monsanto submission date) review by HSD (D.R. Casorso) concluded that "Orally somidobove appears to be innocuous and should present no hazard to man. The adverse dermal, ocular and sensitization reactions were reportedly caused by an impurity in the vehicle." Mentions briefly the existence of two 14-day oral rat studies in an IND which were supplemented by eight additional acute studies in the NDS to determine potential toxicity from accidental human ingestion or contact.

December 15, 1988: Memo by D.R. Casorso identical to the July 18th one but with the recommendation to request rationale from sponsor for limiting the supporting toxicology studies to nine acute and one 90-day sub-chronic study. The issues to be addressed included the following:

- species specificity
- metabolic profile by subcutaneous and oral routes
- effect on hypophysectomized rats
- immunogenicity of somidobove and its breakdown products
- effect of chronic use on composition of milk
- effect on other hormones (levels in blood, milk and tissues)
- effect when administered parenterally and orally to man
- neonatal intestinal absorption
- findings from pertinent published toxicology and pharmacokinetic literature

December 15, 1988: Letter by S. Chopra (A/Chief, HSD) to sponsor conveying the above request.

June 25, 1990: Additional data (A/D) filed in response to a not satisfactory letter, dated May 4, 1989, with respect to efficacy, target animal safety and manufacturing. The response did not include any reference to Dr. Chopra's letter. Nor was this letter mentioned in the May 4, 1989, "not satisfactory" letter.

September 4, 1990: Sponsor submits additional human safety data consisting of.

- Heiman et al manuscript

- article in Science, Aug 24, 1990, pp. 875-884 (summary of FDA's approval)
- internal review of available literature on BST
- subchronic toxicity study in dogs (oral)
- blood levels in dogs after a single sc dose

September 24, 1990: Memo from Yong to Drennan stating that the human safety data are in compliance with the regulations and that the drug is not a hazard to man when used as directed.

Optiflex 640 mg File No. 9460-PI024-505

May 2, 1991: Compliance with respect to human safety and manufacturing mentioned on page 113 of the 116-page review for efficacy and safety in intended species; ADL sent regarding the latter.

March 23, 1992: Director of BVD informed that human safety and manufacturing concerns have been adequately addressed.

October 16, 1992: Concerns were expressed by M. Haydon that the submission has become a political issue and that a scientific decision may not prevail.

May 19, 1994: DG, Food Directorate, informed that the submission satisfies the requirements with respect to human safety.

April 2, 1995: HSD review by M. S. Yong appended to the front of the file.

May 8, 1996: Manufacturer requests submission to be put on hold.

To date: submission remains incomplete with respect to efficacy and target animal safety (potential teratogenicity; direct/indirect effects of rBST on other hormonal systems)

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IND VP-8568 File No. 9460-LOO I 3-502C

Enterokinase linker bovine somatotropin (EKBS)

October 25, 1985: D. Rainnie expressed concern re physiological and toxicological activity of residues of EKBS in milk; possibility of altered (likely increased) levels of non-protein hormones (sex steroids, T3, TO etc). Indicates that residues as measured by a validated method are <1.7 ng/mL- residues are not active orally. Smallest fragment of BST that is active in vitro (rat hepatocytes) is a 37-amino acid peptide; a 14-amino acid fragment of HGH is active intraperitoneally. Neither a 37- nor a 14-amino acid fragment is likely to be absorbed from the gastro-intestinal tract.

Other lines of evidence re human safety: T3, T4, and plasma cortisol levels are unchanged in cows in whom the BST plasma levels are 4-7x normal; GH does not influence the synthesis of estrogens or androgens. Therefore, it was concluded that BST would have no effect on steroid metabolism. Issuance of an ESC recommended.

October 28, 1985: HSD report mentions two 2-week oral studies in Fischer rats; recommends the need for a study in hypophysectomized rats. Mentions reliable limit of detection is 1.7 ng/mL (1.7 ppb) which is in contrast to higher levels reported in the literature. Recommends sponsor be

requested to provide an explanation for this as well as data on non-protein hormone levels; concerns re an impurity.

November 4, 1985: ADL sent from HSD (A/Chief - Mackay)

April 14, 1987: Agreement between BVD and sponsor that data on sex hormone levels in milk is not necessary. Mention that orally administered EKBS to hypophysectomized rats is inactive and that somatotropin levels in milk are similar in both control and treated cows (1-2 ng/mL).

June 17, 1987: letter from BVD to sponsor indicating that the submission is incomplete with respect to efficacy and safety in target animal.

July 2, 1987: Sponsor responds but IND is cleared by DEFAULT (60 day review period expired without any comment from BVD); A/D reviewed by C. Palvilanis who refers toxicity and human safety data to HSD.

Comments:

The human safety aspects of the Elanco submission was cleared by HSD early on in the review process (July 1988) on the basis of limited toxicity data. The nature of the evidence for concluding that foodstuffs derived from BST treated cows present no health hazard to man was not described. As with the Monsanto submission, there were no long term toxicity or reproduction/teratogenicity studies. The issues outlined the December 15, 1988, letter from HSD to the sponsor were not followed up. A rationale should have been provided by the reviewing division as to why this was deemed to be unnecessary. The lack of concern for human safety was reiterated to the BVD Director and Director General Food Directorate, without further additional analysis until the April 1995 HSD review by M.S. Yong.

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Cyanamid ESCs - rBST

June 7, 1984: ESC request from Burton, U. Of Guelph, to Mitchell; in data provided, toxicology section states GH are not orally active; up to 10.0 mg/kg/day rBST for 15 days in rats produced "no changes of toxicological concern"; residue section states that although BST residues were detected in milk (2-4 ppb) with the 25 mg/cow/day dose, this is similar to levels found in high milk producing cows.

June 26, 1984: letter, Mitchell to Burton, requesting target species safety information and if rBST levels in milk from treated cows would expect to be bioactive when orally ingested by humans.

July 10, 1984: memo, Sharma to Haydon, HSD has no problems with ESC;

July 16, 1984: letter, MacKay to Burton, ESC #84205 OK.

September 3, 1985: letter from Mitchell to Kennelly (U. of Alberta) approving ESC #85007; references Sharma memo of 10/7/84 for no human health hazard from consumption of milk from treated cows.

October 25, 1985: same human safety review by Rainnie ; EKBS (enterokinase BST) residues in milk from high dose cows were less than the detection limit of the RIA (1.7 ppb); bGH is not orally active in humans and no bGH is detectable in rat serum following oral dosing; the smallest

active fragment (in vitro) for bGH is a .37 a.a. peptide and it is unlikely a compound of this size would be absorbed from the GI tract; re. possible non-protein hormone increases associated with rBST treatment: cortisol, T3/T4 do not increase when plasma GH increase 4-7-fold; although steroid hormones can be absorbed intact from the GI tract, they are rapidly metabolized; in cows, lactation would be considered as a minor route of excretion; human hypo-pituitary dwarfs treated with GH show no indications of sexual maturation suggesting GH in humans does not induce steroid hormones;

- based on the ESC conditions, milk from rBST cows may be used in foods.
- ESC #85005 issued 30/10/85, Mitchell to Block, with no human health hazard from milk of treated animals.

December 30, 1985: ESC request from McBride to Drennan with approval given (ESC #85024) 23/1/86 quoting standard statement re. Milk and human health.

March 3, 1986: letter from McBride to Mitchell inquiring about the sale of meat from the treated cows and would a 2 week withdrawal period be sufficient; 18/3/86 letter, Drennan to McBride, stating any residues would not be orally active so a 0 withdrawal period applies but if you want to wait for 48 hours go ahead but not required; 18/3/86 letter, MacKay to McBride, saying his initially suggested 2 week withdrawal period would be satisfactory.

2 additional ESCs (#86007 & 86026) issued between April and August, 1986 both citing the original Sharma memo saying HSD has no concerns; Sharma memo slightly modified to include statement that because bGH does not induce growth in human dwarf, HSD has no objections to ESC.

August 11, 1986: report from Cyanamid Canada re- safety and efficacy of sustained-release formulation of rBST; quotes the 15 day gavage study in rats (summary only) and although some absolute organ weights were increased (liver, spleen), it was not dose related and not supported by histopathologic changes.

ESC issued 29/9/86 (#86034) with subsequent letter from Mitchell to Block 2/10/86 stating as drug is not considered orally active, a zero withdrawal period applies for the milk.

Various additional ESCs issued all with standard statement of no HSD concerns.

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Elanco ESCs

1987 trip report, Drennan to Mitchell, re. Dr. Elloit Block's ESCs (#873060) with both Elanco and Cyanamid rBST formulations (recombinant enterokinase linker BST) at MacDonald College, Dept. Of Animal Science, Quebec (60 cow herd) - 2-lactation study looking at milk production, feed efficiency and reproductive performance; preliminary report indicates no significant mastitis problems or milk composition changes but serum progesterone alterations seen related to rBST; indication that progesterone should be analyzed in milk.

ESC signed by Barrett, Dec. 1987, stating human safety division has no objections and milk from treated cows can be used for human food.

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NDS (4VN-862631)

Cyanamid Canada efficacy report: no milk composition changes; 100 and 150 mg/cow/day seems to interfere with normal reproductive behavior - however, daily suggested dose up to 25 mg/cow without effects.

March 30, 1988: toxicology review by BVD (Casorso) for 4VN-862631 NDS; safety in target species not demonstrated, questions relating to species specificity of rBST, milk composition changes, what are rBST and other hormone levels in serum. milk, meat, effect of rBST administration to humans and why toxicology studies were limited to acute, 15-day studies?

Questions partially answered in 7/88 letter from Cyanamid to MacKay with reply back by M.S. Yong on 8/8/89 that the NDS as it relates to human safety can be considered in compliance.

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1996 FDA Veterinary Medical Advisory Committee Meeting Report

- % of raw milk tankers testing positive for violative antibiotic residues has remained fairly constant from 1992-95; no increase in cows treated for mastitis; overall, national U.S. herd size has decreased by approx. 2-5%. Mention of 28-herd study by Monsanto for Post Approval Monitoring Program (PAMP). Statement re. efficacy studies involving i.m. vs. s.c. rBST administration routes not being bioequivalent.

  Note: a Belgium report states that rBST diminishes the severity of induced mastitis; there is a publication which states monoclonal antibodies raised against different rBST epitopes showed increased (approx. 2-fold) in vitro binding affinity towards rBST vs. endogenous BST in serum *(J.Inununoassay, 15*(l):1-19, 1994); however, there also is a fax from one of the authors indicating he doubted that the same technique could be currently applied to milk or used on a commercial basis.

- JECFA rBST concerns from the 22nd CODEX meeting in 1997 were based on MRLs and possible increased risk to viral and bacterial infections in livestock.

- results from the PANT has shown that the incidence of mastitis is slightly increased but less than expected based on the pre-approval studies; also, there is a slight increase in the number of days cows treated with rBST are medicated for all reasons, including mastitis; no specifics are given re. ailments/medications.

- labelling provided with rBST does state that treated cows are at an increased risk for development of clinical mastitis.

- Monsanto PAMP will specifically monitor milk production and drug residues in the 21 top U,S. dairy states (50% of total milk production involved) as well as incidence of mastitis and milk loss pre- and post-rBST introduction due to violative residues.

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rPST (Grolene) Submissions

Toxicology data supplied by the manufacturer stated that PST administered parentally was less

active in humans and not orally active; in a rat gavage study with up to 132 mg/kg/day for 15 days, no physiological changes were noted and no PST detected in blood leading to the conclusion that PST possesses no oral activity.

In another gavage study with IGF-I (0.1, 0.25, 0.5 mg/kg/day) in hypophysectomized rats, terminal body weights were decreased and relative kidney weights increased in mid and high dose females (summary only); not considered treatment related as not dose dependent and only in one sex.

After the last injection of PST to pigs its serum levels remained elevated for 12 hours. No issue was raised about IGF-I.

- IND #5379 approved with respect to human safety, citing a memo of 18/9/90 (Basudde), stating that due to no oral activity of rPST, it should be considered in the same vein as rBST. Neither a Maximum Residue Limit (MRL) nor any withdrawal period was required.

- NDS #6266 submitted data fulfilled human safety requirements and no withdrawal period required (Lambert memo 4/9/92).

- target test species concerns continued to be cited.

Comments:

The physiological actions and functions of PST are similar to those of BST. Like BST, PST was considered to be orally inactive. Also, as with the Monsanto and Elanco submissions, both the Investigational and New Drug submissions for rPST were cleared on limited toxicity data, with no description of the nature of the evidence being provided. Very little mention of IGF-I. HSD expressed no concern regarding human safety as early as 1984. This contention has remained unchanged up to the present time.

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Within BVD Consultations ("Interviews") With Selected Evaluators

Dr. Ian Alexander

In addition to being "File Manager" and the designated spokesperson for all the rBST-related issues at BVD, Dr. Alexander has also been the sole evaluator of the more recent animal safety data for the latest iatrogenic and other relevant outcomes due to this product in the various dairy cattle studies, since 1994.

In a brief meeting with Dr. Alexander Team Members asked him to shed all new, if any, light from these studies on such human safety issues as rBST-related mastitis, antibiotic resistance, milk quality, and teratogenic, reproductive or any other pathological effects. Responding to the Team Dr. Alexander informed that his review of these data was still in progress and thus he was not able to draw any definitive conclusions. (See correspondence: Appendix 2).

Consequently, in the absence of any new animal toxicology indicators toward human safety, the Team wished to hold a short meeting with Dr. Margaret Haydon, particularly since in a pre- 1994 review by her a number of rB ST-treated dairy cows were recognized to have produced certain birth and other iatrogenic defects.

In addition to Dr. Haydon, the Team wished to speak with Dr. Sudarshan Malik, to obtain any personal insights by him about the various mastitis-related surveillance (US) studies, since 1994. Dr. Malik is a generally recognized expert on mastitis-related issues at BVD and he is a member of the rBST Advisory Committee under Dr. Paterson.

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Dr. Margaret Haydon

The types and number of untoward reactions in rBST-treated cows and their offspring was found to be quite extensive. These and other relevant comments by Dr. Haydon were provided to the Team in the form a memo and additional documents (Appendix 3).

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Dr. Sudarshan Malik

The comments that Dr. Malik provided to the Team were simply to state that although he served on the BVD rBST Committee he was not involved in any actual review of this product. The only exception was due to his involvement in the review of the proposed protocol for a Canadian clinical trial on Nutrilac for its risk assessment in cows to cause increased mastitis, in conjunction with Dr. Ken Leslie from the University of Guelph. However, he indicated that, as far he was aware, none of these comments were forwarded to Monsanto. Nor was the intended clinical trial pursued in Canada. He added that the comments that he and Dr. Leslie offered should equally have applied toward the US trials. However, such was not the case, particularly to determine any frequency and intensity of rBST-induced mastitis together with a presumably increased antibiotic use and the thus induced antibiotic resistance (Appendix 4).

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Dr. Cris Basudde & Dr. Gerard Lambert

> The reason for this meeting was to obtain a first hand knowledge and opinions on rBST versus another product, rPST, recombinant porcine somatotropin, which is supposed to cause certain modifications in swine meat production. However, Dr. Basudde who declined to personally meet with the Team was willing to provide a copy of his previously submitted written opinion on this subject to Dr. Paterson (Appendix 5).
>
> Effectively, the human safety issues concerning rBST and rPST were understood to be quite different by both Drs. Basudde and Lambert, due particularly to the fact that rBST was directed toward milk enhancement in cows while rPST was to produce leaner pork. In addition, no issues remained about rPST, since the proposed benefit of this product did not materialize and the relevant submission(s) at BVD were discontinued.

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Additional rBST Material Submitted to JECFA

Vol. 1: addendum I of the EC's BST position paper

Codex Alimentarius Commission (CAQ in 1997 suggested that the scientific data analysis for rBST should be more restrictive as the compound in question doesn't improve herd health but is used for an economic benefit; cite possible concerns re. increased risk of bacterial and viral infections and antibiotic residues in milk (no mention of antibiotic resistance aspect), subtle milk compositional changes and target animal safety (reproductive effects, mammary infections and possible immune system effects).

1. Institut National de la Recherche Agronomique (INRA) report (Hormones, Growth Hormones, Immunity and Retroviral Infections); summarizes bibliography on the subject between 1994 and 1997 (previous report on similar topics had been produced by the same institute in 1993).

The report described general effects of growth hormone on the immune system, growth hormone observations (immune and reproduction) in transgenic mice (bGH gene), growth hormone and effects on prion proteins and lentiviral infections. All experimental data was either based on in vitro observations, endogenously produced bGH (transgenic) or non-oral exposure routes. The main points include:

- rhGH increases phagocytic activity when administered to GH-deficient humans however the biological significance of this is unknown; in general, GH appears to suppress humoral immunity responses but stimulate cell-mediated immune responses;
- PrP (prion protein) expression in vitro can be regulated by a variety of growth factors, including rhGH, dexamethasone, NGF and IGF-I; concentrations required for increased PrP mRNA detection's are 10 ppm for rhGH and 100 ppb for IGF-I;

rBST can affect non-primate lentiviral infectivity in goats; goats infected with CAEV (caprine arthritis encephalitic virus) and treated with rBST (s.c.) exhibit a decrease in the delay period prior to detection of viral expression in milk cells; hypothesized that the mechanism of action involves increased maturation of infected macrophages of mammary epithelial cells;

Based on this data, INRA suggests that there should be an . immunopathological approach to the study of BST effects on latent pathogenic infections in cows (bacterial, viral, prion).

2. 3 articles by P. Willeberg, Denmark Royal Veterinary and Agricultural University, were provided dealing with BST and mastitis.

- a 1993 meta analysis of rBST clinical trials estimated that if 100% of the U.S. herd was being treated with rBST, 20-30% of all mastitis cases after day 60 of lactation would be attributed to rBST; when mastitis incidence is related to cow milk production levels, the relative risk is significantly increased when medium production level control cows are compared to medium production levels treated cows, but not for low and high production cows.

Monsanto response to INRA report:

- there have been no indications from the clinical trials to date that rBST promotes either latent or productive viral replication; GH is often used as a vaccine adjuvant due to its known immunostimulatory effects (promotes lymphoblastogenesis and enhanced cellular immune responses after antigenic challenge);

- cows treated with rBST exhibited an enhancement of the lymphocytic response towards a vaccine comprised of 4 bovine viral antigens; total IgG and IgM production is also significantly increased;
- cows seropositive for bovine leukemia virus (BLV) and treated for up to 255 days with rBST do not develop leukosis or any other symptoms related to BL;
- indications that rBST may be beneficial in the enhancement of cellular immunity during the period of immunosuppression associated with parturition (abstract indicating severity and duration of induced E. *coli* mastitis is reduced in rBST cows);
- calves treated with rBST show no alteration in total lymphocyte numbers or ratio of B to T cells; human GH-deficient infants treated with rhGH give no indications of being at an increased tumor risk;

Volume 2

Monsanto data package submitted to JECFA 50th meeting. Results from PAMP.

1. IGF-I residues in retail milk samples collected from 34 cities in Wisconsin, Minnesota and Iowa; average IGF-I level in milk specifically labeled as from rBST-free cows was 4.3 +/- 0.09 ppb compared to 4.5 +/0.12 in milk not labeled as rBST-6e;

2. No increase was detected in milk discarded due to violative residues in the first 23 months following Posilac introduction (represents surveillance of 52% of total U.S. milk supply); when data are analyzed based on new testing procedures implemented in 1995 for detection of antibiotic residues, it appears that first and third quarter % of milk discarded in 1995 are increased compared to same quarters in 1992-94; results thought to be due to new testing procedures as in 1995 there was no increase in the numbers of cows treated for mastitis, no correlation between average % milk discarded/state and % farms in same states purchasing Posilac and no increase in the sales of mastitis treatment drugs;

3. Under Adverse Drug effects (ADE), no reported increases in abortions in rBST cows (<I.O% in Posilac customers compared to 3.6% U.S. herd average); Posilac package insert does state that use can be associated with reduced pregnancy rates, cystic ovaries, uterine disorders, increased twinning rates and decreased gestation and birth weights;

4. 1997 review article by D.G. Burrin on IGF-I; states after oral exposure in pharmacological doses, IGF-I can induce small intestinal mucosal growth and lactase development in neonatal animals; however, there is limited absorption of IGF-I in biologically relevant concentrations from the GI tract therefore effects on peripheral growth or metabolism would not be expected;

5. Review article by Monsanto on somatotropin (ST) as a homeorhetic regulator of immunity; concludes by stating ST have immunoenhancing effects in domestic animals; although ST can also induce a 10-20% increase in IgG, IgG2 and IgA production, the biological significance of this is unknown.

Volume 3

Additional JECFA-related material; repeat of INRA report including references.

1. Reproductive effects observed in normal and transgenic mice due to bGH include reduced fertility rates and increased abortions; observed at serum bGH levels of 700-2200 ppb or after dosing with 0.3-0.75 mg bGH/day for 3 days (approximately equivalent to cow doses

of 4-9 g/cow). Mechanism of action thought to be related to altered luteal function during early pregnancy due to inadequate prolactin secretion.

2. Treatment of GH-deficient human infants for 6 months with rhGH resulted in an enhancement of monocyte and neutrophil phagocytic activity. There was no observed effects on T or B subset cell numbers or serum immunoglobulin levels.

3. Additional general section on hormonal effects on immune system functionality but no mention of relevance to BST with regards to alteration of other growth promoters.

Volume 4

This volume contains the supplement to the Sept 24/97 BST submission Monsanto filed with JECFA for their review at the 50th meeting in Rome, February, 1998: dated Jan 16/98

The supplement consists of a report by Collier RJ and Kowalczyk DP entitled "Human Health Risk of Retroviruses in Cattle and BST" and 10 supporting references (the latter were not reviewed).

The report discusses the reasons why somatotropin treatment of cattle possibly infected with the bovine immunodeficiency virus, which belongs to the same mammalian lentivirus subfamily which includes HIV-1 and HIV-2 viruses, the cause of AIDS in humans, poses no human health risk. These are:

- impossible to infect human cells in vivo
- antibodies to BLV never found in human serum
- bovine immunodeficiency virus has never been isolated in humans with leukemia
- infectivity of humans with BLV has never been demonstrated

Therefore, BLV is not a human health risk. In addition, CAEV and VISNA, which affect sheep and goats but not cattle, are not known to cause disease in humans.

Transmission of BLV can occur through somatic cells in milk of the infected animal to offspring but can be destroyed by pasteurization. Pasteurization of milk prevents transmission of the virus to any species, including humans.

Fours years of BST use in the US and 8 years in Mexico and Brazil show no indication that the incidence of BLV has increased in cattle.

It should be noted that the studies on pasteurization and infection of human cell cultures date back to the 1970's.

Volume 5

This volume consists of the submission by Consumers International, a 230- member organization in 100 countries: supplementary information dated Sept 25/97

No new original data were presented but scientist reviewed the world literature and submitted studies were not filed and/or which were not considered at the 40th (1992) meeting of JECFA.

Identified potential public health impacts were as follows:

1. Levels of IGF-I are significantly elevated in milk from rBST treated cows and will continue to rise with increased use of *BST*. It is the IGF-I, not the *BST per se*. that is the main cause

for concern regarding possible adverse effects on human health. It is indicated that IGF levels are substantially increased in the latest Monsanto study and in 5/7 studies previously reviewed by JECFA. US FDA concurs that BST treatment leads to statistically significant increases in IGF-I levels in milk. Another study (Prosser et al, 1989) was cited which was reviewed neither by JECFA nor FDA, which reported very high levels (3.6x normal) - much higher than what had been presented in the submitted data. Table I is a good summary of the data.

2. IGF-I, in the presence of casein and other protective factors, is not destroyed by digestion in the stomach and can pass into the intestine, where it may produce local harmful effects. Epithelial cells in the colon grow more rapidly in response to IGF-I at the levels typically found in milk. Acromegaly, a disease involving high endogenous IGF-I levels, is associated with increased risk of colon cancer and pre-cancerous colon polyps.

   It is suggested that toxicity studies with free IGF and the fact that endogenous levels of IGF levels are higher than what is found in the milk of BST treated cows is irrelevant because the IGF is not associated with any protective factors that would ensure bioactivity. IGF binds to receptors lining the GI tract and will stimulate the synthesis of its own receptors. It is also suggested that IGF -1 can be absorbed in the systemic circulation where it may affect the levels of other hormones.

3. Increased mastitis leads to higher antibiotic residues exacerbating antibiotic resistance. The FDA's "safe" limits of up to 150 ppb can select for disease resistance in S. *aureus*.

4. It is speculated that IGF-I plays a role in the expression of genes that encode for prion synthesis and that increased IGF-I shortens the incubation period for Bovine Spongiform Encephalopathy (BSE). Thus, the use of BST might increase the risk of exposure to BSE infection.

Increased IGF-I levels may increase the cows susceptibility to BSE and/or the BST-treated cow's need for increased protein magnifies the odds of exposure to a BSE infective agent. IGF-I leads to increased synthesis of prion proteins. Serum levels of IGF-I (approx. I ug/ml) are at least 2 orders of magnitude higher than those found in milk of BST-treated cows. Thus, the hypothesis can neither be proved or disproved on the basis of the evidence available to date.

It was concluded that there is insufficient information to provide an adequate basis for quantitative risk assessment; therefore, many potential health concerns remain unresolved.

<u>Adverse Effects identified by the 1995 NIH conference:</u>

- local effects on GI tract: both paracrine and autocrine in nature - growth factor for colon cancers -conclude that the colon is at special risk
- strong role in breast cancer
- may play a role in osteosarcoma, the most common bone tumor in children, usually occurring during the adolescent growth spurt
- implicated in lung cancer
- possess angiogenic properties - important to tumors some of which secrete their own growth factors to promote angiogenesis,
  e.g., retinal neovascularization in mice

  NIH 1991 conference recommended that the acute and chronic effects of IGF-I be determined in the upper GI tract

90 references were cited - these were not reviewed

Variability of the mastitis effect means that global averages hide the fact that some one third to one half of the herds are hit heavily by mastitis: BST-induced mastitis is harder to treat than naturally occurring mastitis and duration of treatment is longer due to higher incidence of infection with S. aureus. BST use is associated with extensive off label use of antibiotics not approved for treating mastitis because those that are approved are relatively ineffective. There is a one-third higher incidence of antibiotic resistant bacteria. BST use increases the amounts of drugs in general to treat the various adverse effects it causes in cattle.

US figures on violative antibiotic residues understate the true incidence of residues. Spot checks likely miss many drugs in use. The existing antibiotic testing program cannot guarantee that illegal residues are not present in* the milk supply. There is no direct evidence, either from the studies submitted to the FDA or in the PAMP, because no data were obtained from treated and untreated cows directly.

Volume 6

Compilation of numerous reports documenting potential adverse human health effects submitted by the European Commission, October 29, 1997

Article by SS Epstein, 1990

Report by Epstein. Kronfeld and Challacombe prepared for the Green Network UK and Cancer Prevention Coalition

Position Paper of the Toronto Food Policy Council, August, 1997 This contained allegations of

- incomplete regulatory evaluation (no chronic toxicity studies, failure to properly evaluate the potentially negative health impact of IGF-I);
- questionable scientific and statistical analysis of potential human health impact;
- regulatory agency takes industry results in good faith without critical analysis;
- measures to protect the integrity of the dairy breeding programs are lacking; and
- people consume more BGH and IGF-I than the research suggests - no evidence to support the contention that IGF-I is denatured by commercial pasteurization practices used in Canada even if it is destroyed by the processes used in preparing infant formulas, this still leaves the majority of Canadians drinking milk which has not undergone such processes to destroy IGF-I.

The position that the Toronto Food Policy Council adopted was as follows: (a) approval not -be granted pending resolution of above issues, (b) chronic toxicity (at least 2 years) and reproductive (two generation) studies need to be conducted to ensure the lack of a possibly long latency period (effects may not appear until after 18 months) and (c) relevant risk assessment techniques and methodologies be applied, which comprises relevant scientific evidence, relevant process and production methods and relevant inspection, sampling and testing methods.

Three articles by P Willeberg, another by SS Epstein, a good overview of Vorrall (UK), 2 articles by Scholfield and Mepham - no new information was introduced.

Comment:

Simply not enough is known about how IGF-I functions to properly evaluate the potential health impact.

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HUMAN SAFETY DATA REVIEWS AND GAPS

The mandate of this review Team was not to evaluate actual data and/or opinions but to conduct a "gaps analysis" on what needed to be done by BVD (HSD) in contrast to what was actually done in order to come to the conclusion that rBST (Nutrilac) posed no hazard to human health as assessed under the exigencies of the Food and Drugs Act & Regulations. The standard requirement for any New Drug is a data package which includes acute, subacute and chronic studies, 2 generation reproduction studies, teratology studies, other special studies depending upon the physiological properties of the drug as well as residue studies to support withdrawal periods. The use of BST, as any other growth hormone, is solely for economic purposes. The submission in support of BST was unique in that the usual data package was not filed. The Nutrilac documentation was an abbreviated submission in which many of the usual toxicity studies and certain special studies regarding oral absorption and hormonal or immunological effects were lacking.

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WHAT WAS DONE

For the purpose of approving ESCs, HSD concluded that the milk and meat from BST treated cows was safe for human consumption as early as 1986, without providing any rationale as why this conclusion was reached. Studies submitted in support of this conclusion were not described until 1990.

1990: 4-page review by D.R. Casorso completed within two weeks of the filing of the submission.

1995: more detailed review by M.S. Yong which presented, for the first time, the rationale for concluding that meat and milk from BST -treated cows is safe for human consumption; first mention of the potential adverse health effects of IGF-I.

1998 reviews by M.S. Yong: rationale for waiving the need for chronic toxicity testing; discussion of potential allergenicity.

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WHAT WAS NOT DONE

Studies indicated by manufacturer as being available upon request were never requested by HSD reviewers.

Importance of the 3-month rat toxicology study as an indicator of potential oral absorption

of rBST, i.e., the demonstration of immunoglobins in rat serum, was not mentioned. This is an important omission in that the lack of oral bioactivity formed the basis for waiving chronic toxicity study requirements. The human health implications of the immunological findings in rats should have been thoroughly evaluated and dismissed only if adequately justified by the evidence available at the time (e.g., binding of rBST to HG receptor is negligible; antibodies raised to rBST will not cross react with HG, primary response was induced in only 30% of animals at high doses, etc.). IGF-I production in liver of rats was not examined. Species specificity issues and possible threshold effects (dose -response) should have been discussed. Secondary challenge bioassays should have been requested to further characterize the immunological response.

The fact the rBST can be absorbed, albeit at high doses, calls into question the decision not to request additional chronic toxicity studies. The evaluator should have explored the physiological effects of such high oral doses (and effects on hypophysectomized rats further (e.g., effects on peripheral growth and metabolism).

The 1990 evaluation was largely a theoretical review taking the manufacturer's conclusions at face value. No details of the studies nor a critical analysis of the quality of the data was provided.

The requirement for a 3-month study in a nonrodent species (e.g,, dog) was not requested. No long-term toxicology, teratology or reproductive/fertility studies were requested. Definitive studies demonstrating the lack of absorption of rBST or IGF-I upon oral administration were neither conducted nor requested.

Potential adverse effects of IGF-I on human health were not discussed until 1995. When discussed, rationales were based purely on speculative reasoning and not on substantive data or studies. The rationale for not requiring chronic toxicity or teratology/reproductive studies was described in more detail in the 1998 reports but again is based on the assumption that there are no physiological consequences of oral absorption of rBST. This ignores the fact that the 3-month rat study did show a physiological response.

Evidence from the animal safety reviews were not taken into consideration. These studies indicated numerous adverse effects in cows, including birth defects, reproductive disorders, higher incidence of mastitis, which may have had an impact on human health. This observation should be qualified by the poor quality of the data package. Similar observations were recorded in the FDA FOI summary and the company label. These findings should have stimulated the need for requesting additional teratology and reproduction studies in laboratory animals. This should have prompted HSD evaluators to re-examine the accuracy of their data and the assumptions based thereon.

The mastitis issue should have raised concerns regarding increased use of antibiotics with consequent exacerbation of resistance to antibiotics.

The nature of the product (being a hormone) and its chemistry should have prompted more exhaustive and longer toxicological studies in laboratory animals.

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GAPS IN THE SCIENTIFIC DATA

The procedures followed by BVD, were not too dissimilar from those followed by the US FDA, both of which have come under criticism.

Somatotropins require binding to receptor sites to exert their mechanism of action. It is known that BST possesses limited binding affinity to the human receptors for growth hormone. Therefore, adverse effects from exposure of humans to BST would not be anticipated. However, actual proof that the operative underlying assumptions are correct was not provided. The data should have been provided in sufficient detail to permit independent analysis rather than in the form of peer reviewed articles, recognizing that the latter do not necessarily guarantee consensus.

Concerning IGF-I, Monsanto did not submit any studies in hypophysectomized rats - this information was gleaned from the files of another manufacturer (Elanco). Proprietary information from one manufacturer is not used to support the submission of another manufacturer.

Since the date of its filing, the handling of the Mosanto submission has been highly controversial: unilateral decisions appear to have been made with respect to who holds the file, who conducts the review, who is excluded from the review, who attends and who appoints the Canadian representative to the JECFA conference.

The validity and accuracy of the PAMP data is currently being analyzed by BVD. Hence, the committee cannot comment on the results presented to JECFA by Monsanto, in which it is contended that there is no increased incidence of mastitis. This should be taken into consideration only after all the other human safety issues have been resolved.

Sub-chronic Toxicity

According to a four-page review on Monsanto's Nutrilac submission, signed respectively by Drs. D.R. Casorso and M.S Yong, on March I and March 7,1990, the following notes and views were recorded:

90 Day rat, 0.1, 0.5, 5.0 and 50.0 mg/kg/day by oral gavage for the treatment rats, and 1.0 mg/kg/day subcutaneous for control animals. No Effect Level (NEL) was assigned at 50.0 mg/kg/day.

Chronic Toxicity

No laboratory animal chronic toxicity studies were submitted.

However, it was added that:

> "The Manufacturer submitted the following (17 items). Each was referenced to a published research paper or supported by a Manufacturer's research report. This Evaluator does not question the veracity of the submissions".

Among the Manufacturer's research reports, item # 14 which presumably referred to above mentioned "Subacute Toxicity" study contained the following comments:

> "Oral sometribove (Nutrilac) at 100 to 50,000 ug/kg/day (0.1 to 50.0 mg/kg/day) for three months produced no changes in the treated rats."

An obvious implication of these comments was that as much as 50 mg/kg/day orally administered doses of rBST (Nutrilac) to rats for up to three months produced no effect and,

as such, it was not and could not be absorbed via the oral route in any species and for any length of time.

However, the review did not record a duly reported effect in that, it produced an rBST-specific immunoglobulin response in at least 20 percent of the orally treated rats on 5.0 mg/kg/day and 30 percent on 50.0 mg/kg/day, as compared to 95 percent on I mg/kg/day by the subcutaneous route. According to these observations not only was the orally administered rBST absorbed into the blood stream of these rats but also that it produced in them a distinct immunological effect. See Table I and Appendix 6 and 7.

Table 1. DETERMINATION OF BST IMMUNOGLOBULINS IN RAT SERUM

Treatment		Week 7	Week 14	Week 28
Control	(No BST)	0/20	0/30	0/10
Inject BST	I mg/kg/day	19/20	27/28	9/10
Gavage BST0.	1 mg/kg/day	0/20	1/30	0/10
Gavage BST	0.5 mg/kg/day	0/20	0/29	0/10
Gavage BST	5.0 mg/kg/day	4/20	6/30	0/10
Gavage BST	50 mg/kg/day	3/20	9/30	2/10

The oral absorption and its consequent immunological response in rats were neither recorded nor commented upon in the above mentioned BVD review by Drs. Casorso and Yong in 1990. Nor did these appear to enter in to any kind of discussion in the US FDA Summary review, under Freedom of Information. However, in contrast to the BVD and FDA review, the immunological effect in these orally administered rats with rBST was noted in the European Commission Report.

It should be noted that for a separate New Drug Submission on a virtually identical rBST product (Somidobove) from Elanco Canada, which also was evaluated by Dr. D.R. Casorso but in conjunction with Dr. Shiv Chopra, as Acting Chief of Human Safety Division, an altogether different set of questions and concerns were communicated to this particular company.

The manufacturer was asked to, address the following issues:

- rationale to limit toxicology to only acute and sub-chronic studies
- species specificity
- metabolic profile by subcutaneous and oral routes
- effect on hypophysectomized rats
- immunogenicity of somidobove and its breakdown products
- effect of chronic use on composition of milk
- effect on other hormones (levels in blood, milk and tissues)
- effect when administered parenterally and orally to man
- neonatal intestinal absorption
- findings from pertinent published toxicology and pharmacokinetic literature

To officially convey these views and concerns to the manufacturer an "Additional Data Letter" was issued on December 15, 1988, by Dr. Shiv Chopra (A/Chief, HSD).

Additional data was filed, June 25, 1990, in response to a not satisfactory letter, dated May 4, 1989, with respect to efficacy, target animal safety and manufacturing. The response did not include any reference to Dr. Chopra's letter. Nor was this letter mentioned in the May 4,

1989, 'not satisfactory" letter.

Additional data and reviews gaps were discovered in the highly critical areas concerning: Food Safety Overview; and Drug Residue Depletion Studies, involving IGF-I studies. Only abstracts of published papers, without the accompanying raw data, were submitted. The data were offered, if requested (Appendix 8). However, this did not occur which indicates that the data were at face value, without the required review and evaluation at BVD.

With respect to these other toxicology concerns, particularly about certain drug-related birth defects and other derangement's of the reproduction system, certain warning signals appeared to be raised in the target animal safety reviews by Dr. Margaret Haydon. However, none of these stimulated any concern or response from the Human Safety Division of BVD.

A similar approach was followed by the US FDA, as outlined in their summary review on "Posilac" (Nutrilac). This product was approved in the U.S. in 1994. The only restriction by the FDA was to require approximately twenty different rBST-related adverse reactions in the treated cows on the product label.

One human safety concern that FDA did yield to was the potential to face an rBST-induced increase of mastitis in the treated cows and a concomitant increase of antibiotic treatment of same, to produce "violative residues". However, this particular concern was deferred to an automatic control via the field monitoring of "violative residues" in the bulk milk supply. Evidently, considering that during the experimental trials of rBST in dairy cows the relative frequency of mastitis was reportedly increased by approximately fifty percent, the field monitoring of "violative residues" in the bulk milk supply of the affected cows would fail to address the issue of a concomitantly occurring larger use of antibiotics and the thus associated antibiotic resistance in the farm-borne human pathogens. It should be noted that the issue of mastitis, use of antibiotics and discards of bulk milk due to violative residues is currently under review.

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Product Label

The use of Nutrilac in lactating dairy cows is admittedly associated with serious and complicated problems. Certain of these problems, such as the relatively greater incidence of mastitis, antibiotic treatments and the thus arising bacterial resistance in farm-borne human pathogens, and others indicate a critical but unknown risk of this product to human safety. Apart from mastitis and antibiotic resistance, progressively increasing inflammatory lesions and reactions due to rBST injections to cows are declared on the label. However, the position that the manufacturer proposed that despite of these reactions and problems in cows neither the quality of their milk nor any other human health risk will follow. For a copy of the label see Appendix 9.

The thus far conducted evaluation at BVD did not address any of. these parameters of human safety. It represents a serious gap, requiring critical analysis.

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"GAPS-ANALYSIS"

The fundamental mandate of the Human Safety requirements of the Food and Drugs Act and Regulations toward any veterinary drug prescriptions for food producing animals is to enlist each and every associated risk to human health and thereby limit its real and potential dangers to both society and the individuals within. This does not appear to have properly been followed toward the risk assessment of any rBST product, including Nutrilac, by the Human Safety Division of the Bureau of Veterinary Drugs.

The only short-term toxicology study, for three months in rat, was improperly reported, to conclude that rBST (Nutrilac) was not and could not be absorbed into the blood stream.

The usually required long-term toxicology studies to ascertain human safety were not conducted. Hence, such possibilities and potential as sterility, infertility, birth defects, cancer and immunological derangement's were not addressed.

Virtually no attention appears to be directed toward a critically anticipated increase in rBST related infective mastitis in dairy cows and also the concomitantly expected increase in antibiotic therapy and antibiotic resistance in the farm-borne pathogens of humans.

Finally, apart from all the afore-mentioned issues, one cannot be oblivious to the manner in which all the various rBST-related reviews and commentaries were allegedly produced at both BVD and its counterpart, Center for Veterinary Medicine, at US FDA. Duly arising from this particular issue certain senior officials of both these agencies have allegedly been asked to be investigated for employing unauthorized influence against subordinate staff and a personal "conflict of interest" (Appendix 10).

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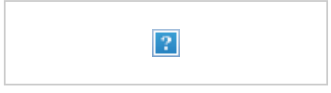

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April 21, 1998

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APPENDIX V

DETERMINATION OF SOMETRIBOVE

IMMUNOGLOBULIN IN RAT SERUM

INTRODUCTION:

Monsanto Company undertook a 3-month gavage study at the request of the CVMP to confirm the absence of oral activity of sometribove. (1) A 4-week study had been conducted earlier showing that sometribove was not orally active when administered at doses up to 6,000 ug/kg/day to rats. (2)

In the 90-day study experimental design, there were 30 rats/sex/treatment group. Fifteen rats/sex/group were used only for blood collection to determine whether antibodies to sometribove could be measured in rats dosed orally or by daily subcutaneous injection (positive controls). The examination for antibodies was prompted by reports of detection of circulating anti-BST antibodies in hypophysectomized rats administered pituitary BST orally or by injection. (3) We were uncertain whether these investigators had actually detected antibodies since they had not examined pre-test blood samples for the presence of serum proteins that could have interfered with the assay. Secondly, we were not certain if hypophysectomy had altered the permeability of GI tract to proteins of affected in some unknown manner the responsiveness of the immune system since they reported defecting antibodies after only 9 days of treatment. In our 90-day study, 5 of the 15 animals/sex/group in the blood collection group were randomly designated as recovery animals and were held for approximately 14 weeks after the termination of the study. After 14 weeks of sometribove treatment, and 14 weeks without treatment, the recovery animals were sacrificed and blood collected for antibody determination.

Prior to study initiation, blood was collected from all 15 rats/sex/group in the blood collection group for determination of baseline antibodies (pre-immune serum). At 7 weeks into the study, blood from 10/15 animals (does not include 5 rats/sex/group recovery animals) was collected for antibody determinations and a study termination, blood was collected from all 15 rats/sex/group (including recovery animals) for antibody determination.

Analytical Methods

To accurately measure the production of sometribove immunoglobulins following

sometribove treatment, a sometribove positive control serum was developed in rats by injection of sometribove in Freunds adjuvant according to standard immunization protocols. Sometribove immune positive and immune negative serum was used to validate an assay which specifically measures antibodies to sometribove in rat serum. In this assay, 50 ul of rat serum incubated overnight at room temperature with 300 ul of 125I-sometribove (0.35 ng sometribove/tube), to permit the binding of 125I-sometribove to the antibodies present in rat serum. The antibody 125I-sometribove complexes were specifically precipitated by adding 100 ul of goat anti-rat gamma globulin. This precipitation procedure is specific for rat immunoglobulins and preferentially reacts with antibody of the G subclass. Following centrifugation, the radioactivity in the pellet is corrected for nonspecific binding. The sometribove antibody titer is expressed as a percent of the corrected cpm divided by total cpm.

RESULTS AND DISCUSSION

Between week 1 and week 7, there was an increase in sometribove binding capacity in control rat sera. Therefore, the sometribove binding capacity of samples from the control animals in the treatment and recovery periods was used to determine a range of sometribove binding in normal rats. In normal rats, an upper sometribove binding capacity limit of 11% was calculated as the 75% percentile plus 1.5 times the interquartile range. Animals with greater than 11% sometribove binding capacity were considered antibody positive.

Table 1 summarizes the results of the antibody titer analyses. As expected, none of the sera from control rats showed positive sometribove binding. On the other hand, all but one of the rats injected with sometribove developed antibodies by week seven, and these antibodies persisted at approximately the same titer throughout the treatment period (week 14). In the recovery blood sample, drawn about 14 weeks after the last sometribove injection, these sometribove antibodies titers were decreased (Table 2).

At week 7, sometribove antibodies were not present in serum from rats in the two lower oral gavage groups (100 ug/kg/day and 500 ug/kg/day). At week 14, one rat in the lowest gavage group had developed sometribove antibodies. Since no antibodies developed in the 500ug/kg/day group,it seems likely that the one positive rat in the 100ug/kg/day group is either an extremely hypersensitive animal or more likely attributable to a mislabelled sample.

Gavaging rats with excessive, non-pharmacologic doses of sometribove (e.g. 5000 and 50,000 ug/kg/day) produced antibodies in a few rats. The percentage of rats with antibodies (15-20%) was similar in both of these dosage groups at 7 weeks. No increase in the percent of rats with antibodies was evident at the 5000 ug/kg/day dosage level at week 14; a slight increase in rats exhibiting antibodies (30%) was evident at the highest dosage tested at 14 weeks.

Following cessation of treatment, there was a decline in the antibody titers for the positive control recovery rats (Table 2). Of the rats exhibiting antibodies in blood at the 14-week terminal sacrifice, only 2 animals in the highest dosage group were recovery animals. The other recovery animals did not exhibit antibodies at the 14-week terminal blood collection. The two recovery animals in the highest dosage group that exhibited antibodies at 14 week had reduced titers following 14 weeks of recovery (week 28 - Table 2).

Since the measurement of antibodies was performed with intact sometribove, the antibody positive rats were probably exposed to intact sometribove and not fragments which would not have the appropriate tertiary structure to generate antibodies to cross react with intact

sometribove.

It is conceivable that at the highest dosage tested, the bolus administration of sometribove presented a sufficient antigen load to the gut to induce antibody production. Such exposures would not occur from consumption of meat/milk from sometribove treated dairy cows since the levels of residual sometribove are in the ng/gm or ppb range. It cannot be ruled out that local trauma to the esophagus or stomach from daily intubation of rats may have broken the epithelial barrier and permitted absorption of small amounts of sometribove. Alternatively, small amounts of sometribove could have leaked into the lung during daily intubation which could have been absorbed systemically to generate antibodies.

There does appear to be a threshold dose for antibody production since (with the exception of the one questionable response at the lowest dose), no antibodies were detected in rats administered 500 ug/kg/day sometribove. In the investigation with hypophysectomized rats previously alluded to, the "no effect" level for antibodies was considered to be 400 ug/kg/day. (3)

One may question the significance of the presence of antibodies in the rats exposed to higher doses of sometribove since there was no evidence of changes in growth, clinical parameters or gross and microscopic pathology in rats administered up to 50,000 ug/kg/day sometribove.

There is a considerable body of literature demonstrating that oral administration of large amounts of foreign food proteins (e.g. bovine milk caseins, lactoglobulins, lactalbumins, egg white protein) to laboratory animals or humans can induce the formation of circulating IgG and other antibodies. (4, 5) Indeed, most children and some adults carry antibodies to these same bovine milk proteins as well as a multitude of other dietary proteins that we are exposed to. Thus, the detection of anti-sometribove antibodies in rats administered large amounts orally is a normal physiologic response. Humans will be exposed to much smaller amounts of sometribove, which based on the rat data, will be far below a level which can generate an immunologic response.

TABLE 1. DETERMINATION OF BST IMMUNOGLOBULINS IN RAT SERUM

Treatment	Week 7	Week 14	Week 28 (Recovery)
Control	0/20	0/30	0/10
(No BST) Inject BST	19/20	27/28	9/10
(1 mg/kg/day) Gavage BST	0/20	1/30	0/10
(0.1 mg/kg/day) Gavage BST	0/20	0/29	0/10
(0.5 mg/kg/day) Gavage BST	4/20	6/30	0/10
(5 mg/kg/day) Gavage BST	3/20	9/30	2/10
(50 mg/kg/day)			

1Number of animals with percent antibodies greater than 11/total number of animals.

TABLE 2. IMMUNOGLOBULIN TITERS IN RATS AT WEEK 14 AND WEEK 28 (RECOVERY)

Treatment	Titer Week 14	Titer Week 28
Inject BST 1 mg/kg/day		
Rat 6159	70%	17%
6160	58%	13%
6161	87%	75%
6162	83%	55%
6163	85%	45%
6189	80%	43%
6190	60%	17%
6191	33%	11%
6192	28%	9%
6193	64%	14%
Gavage BST 50 mg/kg/day		
Rat 6431	28%	19%
6433	81%	67%

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LISTING OF INVIDUAL DATA VALUES FOR BST BINDING CAPACITY OF RAT SERUM

TRT RAT WEEK BST BINDING TRI-TREATMENT

1 6089 1 3.813202	TREATMENT 1: CONTOL (NO BST)
1 6089 14 7.3 877 ?	TREATMENT 2: INJECT BST 1 MG/KG/DAY
1 6089 7 6.984155	TREATMENT 3 GAVAGE BST .1 MG/KG/DAY
1 6090 1 3.64768	TREATMENT 4 GAVAGE BST .5 MG/KG/DAY
1 6090 14 7.323877	TREATMENT 5GAVAGE BST 5 MG/KG/DAY
1 6090 7 6.312148	TREATMENT 6GAVAGE BST 50 MG/KG/DAY
1 6091 1 3.399708	
1 6091 14 7.075905	
1 6091 7 7.109381	
1 6092 1 3.898133	
1 6092 14 9.726734	
1 6092 7 9.003893	
1 6093 1 4.377769	
1 6093 14 7.887367	
1 6093 7 7.878456	
1 6094 1 2.917027	
1 6094 14 8.232344	

1 6094 7 8.231071
1 6095 1 3.981873
1 6095 14 9.655532
1 6095 7 7.868272
1 6096 1 4.272111
1 6096 14 10.21564
1 6096 7 9.105606
1 6097 1 4.518397
1 6097 14 8.743606
1 6097 7 7.933849
1 6098 1 4.438437
1 6098 14 9.402328
1 6098 7 8.581147
1 6099 1 4.30363
1 6099 14 7.642851
1 6099 28 6.861919
1 6100 1 4.227392
1 6100 14 7.613626
1 6100 28 6.357558
1 6101 1 4.640983
1 6101 14 8.321368
1 6101 28 7.222384
1 6102 1 3.330326
1 6102 14 8.010063
1 6102 18 7.421512
1 6103 1 4.602229
1 6103 14 7.608544
1 6103 28 8.106105
1 6119 1 5.4642
1 6119 14 8.116773
1 6119 7 8.725437
1 6120 1 4.736559
1 6120 14 8.297118
1 6120 7 8.437386
1 6121 1 4.739063
1 6121 14 8.48122
1 6121 7 7.445489
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1 6122 14 10.78813
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2 6161 14 87.24921
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