

REPLACEMENT PAGE 1

THERAPEUTIC GOODS ADMINISTRATION AUSTRALIA

PRECLINICAL EVALUATION OF APPLICATION FOR REGISTRATION

Sponsor:	Amersham Australia Pty Ltd
Drug Name:	strontium [⁸⁹Sr] chloride injection
Brand Name:	METASTRON
Dose Form:	injection, intravenous
Strength:	single dose vials of 150 MBq in 4 mL (equivalent to 1 mCi/mL)
Evaluator:	XXXXXXXXXXXXXXXXXXXX
File No.	88/03429
Control No.	90-2-639

NOTE: This evaluation and addendum have been checked for confidential material and are cleared for release to the sponsor providing that pages 1, 3 and 17 are substituted with the replacement pages attached.

SUMMARY AND ASSESSMENT

1. The application is for registration of strontium [⁸⁹Sr] chloride injection (METASTRON) to be indicated for "the palliation of pain from bone metastases secondary to prostate carcinoma in patients who have not responded, or who are no longer responding to conventional therapies including external beam radiotherapy." This radiopharmaceutical is for therapeutic use and not for diagnostic use.
2. Dose recommended is one vial of 150 MBq (4 mCi) per injection. "Alternatively in particularly heavy or light framed patients a dose of 2 MBq (55 µCi)/kg 'fat-free' body weight may be used. Repeat administration should not be performed within three months of the previous METASTRON injection. Further administrations are not indicated in patients who have not responded to a previous administration of METASTRON."
3. The potential maximum single dose of strontium could be 73 mg which, for a 50 kg person, would be 1.46 mg/kg.
4. Strontium-89 decays by β⁻ beta emission at 1.463 MeV (100%). It has a physical half-life of 50.5 days.
5. Submitted studies did not have GLP certification.

6. Strontium is known to mimic calcium in most biological reactions but no pharmacological studies were submitted. No preclinical data were available to justify the pharmacological efficacy of strontium-89 as an analgesic in painful bone metastases. The therapeutic use must rest on human pharmacological effect.
7. Distribution of strontium (usually strontium-85 a gamma emitter) following an IV dose was shown to be rapidly and almost exclusively located in bones with retentions at 2 days of 50-60% in rats, and about 26-50% in rabbit skeleton. Less than 1% (total) was retained in all other tissues. Newly forming bone (metaphyses), fracture callus material and trabecular bone, accumulated radiostrontium preferentially. Initial retention of strontium was inversely related to the age of the animals, and inversely related to calcium content of the diet. Distribution of strontium-89 appeared to be identical to that of calcium-45.
8. Excretion of radiostrontium was rapid over the first 2 days following an IV dose. In urine this amounted to 40% of the dose (for rat), 54% (for mouse) and 70% (for rabbit). Two weeks after a parenteral injection, excretion of strontium-89 was less than its rate of physical decay. Skeletal areas of lesser bone turnover (remodelling) retained strontium for the greater time.
9. Acute toxicity of non-radioactive strontium was lower than for calcium: the IV LD₅₀ being 148 (mouse) and 123 mg/kg (rat).
Strontium-89 in mice gave an LD₅₀ at 30 days of 8 mCi/kg.
10. Aplasia of mouse bone marrow was seen at 14 days after a single injection of strontium-89 at 3 mCi/kg. Spleens became enlarged and extremely active with myelopoiesis. These mice showed raised susceptibility to infection with Friend leukaemia virus and *Listeria monocytogenes*. Marrow damage with an increased risk of infection during human therapy with strontium [⁸⁹Sr] chloride must be considered.
11. Bone tumours appeared to be the cause of death for about 7% of mice at 200-250 days after a single dose of strontium-89 of 5 mCi/kg. These tumours also developed in rats within about 8 months after 10 daily injections of strontium-89 at as little as 0.05 mCi/kg (total dose of 0.5 mCi/kg). This dose is only about 9 times larger than the proposed clinical dose.
12. Bone tumours in humans must be considered a risk of therapy with strontium-89. However, the benefit may be considered to outweigh the risk in patients needing pain relief from bone metastases during terminal stages of cancer where alternative treatment has been unsuccessful. The carcinogenic risk may need to be stated as part of the benefit-to-risk estimation before the use of strontium-89.
13. Young animals, because of their actively growing bones, appeared to be at an high risk of bone tumours caused by radiostrontium. Children, with their potentially longer life span, should be excluded from treatment with strontium [⁸⁹Sr] chloride unless alternative therapy was unsuccessful.

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14. Genetic toxicity studies were not submitted. Strontium-89, being a strong beta emitter, must be considered to be genotoxic.
15. Strontium-89 is known to cross the placenta and to be secreted in milk. Strontium-89 may be expected to cause fetal bone marrow damage and initiate fetal bone tumours.
16. Although the product is not intended for use in women in Australia, overseas usage and trials include bone metastases secondary to breast cancer. As these reports may encourage such use here, a warning against its use in pregnancy should be included in the PI. Similarly, the PI should warn against its use in nursing mothers and in children.
17. Risk of drug use in pregnancy should be listed as Category D.

RECOMMENDATION

Preclinical data show the use of strontium [⁸⁹Sr] chloride (METASTRON) to carry a risk of toxicity. Its use should take note of the following:

No preclinical data were available to justify the pharmacological efficacy of strontium-89 as an analgesic in painful bone metastases. The therapeutic use must rest on human pharmacological effect.

Strontium [⁸⁹Sr] chloride may show toxicity to bone marrow increasing the risk of leucopenia and of serious infection. Cell counts should be kept under review.

Exaggerated doses of this drug used in animals have caused osteogenic sarcomas, and the lower doses used clinically may not be free of this problem. Although its use will be in terminally ill patients suffering pain from bone metastases, it may be prudent to restrict its use to cases where alternative treatment has been unsuccessful.

The following warning is suggested for the Australian PI:

"Categorisation of risk of drug use in pregnancy is Category D. Strontium [⁸⁹Sr] chloride (METASTRON) is not to be administered to pregnant women or nursing mothers."

XXXXXXXXXXXXXXXXXXXX

Drug Evaluation Branch

27-4-92.

STRONTIUM [^{89}Sr] CHLORIDE (METASTRON) INJECTION - AMERSHAM

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STRONTIUM [⁸⁹Sr] CHLORIDE (METASTRON) INJECTION - AMERSHAM

1.0 INTRODUCTION

1.1 Formulation

METASTRON is a sterile aqueous solution of strontium [⁸⁹Sr] chloride at a total strontium content of 24-50 mg and 150 MBq in 4 mL (equivalent to 4 mCi). The single dose vial is sterilised by autoclaving and does not contain preservative or other excipient. It is not intended to be diluted. Expiry life is stated as: "the product should not be used later than 4 weeks after the activity reference date."

1.2 Indication

METASTRON is an intravenous injection to be indicated for "the palliation of pain from bone metastases secondary to prostate carcinoma in patients who have not responded, or who are no longer responding, to conventional therapies including external beam radiotherapy." This radiopharmaceutical is for therapeutic, not diagnostic, use.

1.3 Dosage

The recommended dose is one vial of 150 MBq (4 mCi) per injection. "Alternatively in particularly heavy or light framed patients a dose of 2 MBq (55 µCi)/kg 'fat-free' body weight may be used. Repeat administration should not be performed within three months of the previous METASTRON injection. Further administrations are not indicated in patients who have not responded to a previous administration of METASTRON."

From the likely maximum strontium content (weakest specific activity) mentioned under Formulation (above) the dose of strontium at the reference date could be 50 mg. By the time of 4 weeks (expiry life) at the physical half-life of 50.5 days, the Company calculates that the 150 MBq could result in a maximum dose of 73 mg strontium. For a 50 kg person this would be 1.46 mg/kg.

1.4 Generic name

There is no separate officially recognised generic name in AAN, BAN or USAN. This evaluation employs the standard chemical terminology of **strontium [⁸⁹Sr] chloride**.

1.5 History

Strontium [⁸⁹Sr] chloride, administered for the current indication, was initially reported by Pecher, C (California) in 1942, and then from 1976 onwards in the American and European literature. The current product has been registered in Canada, July 1986; in the UK, November 1989; and in Sweden, March 1990. Applications are pending in Denmark (1986) and in the EEC with the multistate procedure (1990). An IND is in progress in the USA.

1.6 Physical properties of strontium-89

Type of decay: β^- beta emission at 1.463 MeV (100%).

Half life: 50.5 days

Range of β^- : 0.8 cm average in tissues.

Strontium [^{89}Sr] decays to stable yttrium [^{89}Y].

Radionuclidic purity for total detectable gamma emitters is claimed to be not more than 0.4% at reference or expiry date.

2.0 PHARMACOLOGY

It is generally known that strontium resembles calcium and that it may take the place of calcium, such as in Ringer-Locke solutions and in the blood clotting cascade, and that it generally appears weaker and less toxic than calcium. No preclinical data were available to justify the pharmacological efficacy of strontium-89 as an analgesic in painful bone metastases. The therapeutic use must rest on human pharmacological effect.

Human studies are available that report the effect of strontium-89 treatment on serum alkaline phosphatase, serum acid phosphatase and on prostate specific antigen in prostatic cancer. No preclinical reports covering these items in animal models were submitted.

3.0 PHARMACOKINETICS

The Company carried out one study in mice with strontium-85 (a gamma emitter) as a model for strontium-89 but no other specific preclinical study under this heading. Literature reviews were submitted. There was no preclinical estimation of **dosimetry**. One gains the impression that the human dose may be the maximum compatible with bone marrow survival in most cases.

3.1 Absorption

There is no requirement for preclinical study of bioavailability as the clinical route of administration is IV.

3.1.1 Mice

Paper by Rozing, J., Buurman, WA & Benner, R (1976) Cellular Immunology 24: 79-89. The authors stated that their experience (reference to a 1962 paper) had shown: "strontium-89 injected IP results in 1.5 times more skeletal deposition of the isotope as compared with IV injection." This does not appear to have been further tested in the preclinical data available to this evaluator.

3.2 Distribution

3.2.1 Mice

This was the initial paper by Pecher, C (1942) University of California Publications in Pharmacology 2: 117-149. A-strain mice were injected IV with strontium [^{89}Sr] lactate and then various analyses carried out.

The author found a rapid localisation of the isotope into the skeleton, tending to plateau by 5 hours post injection, at 20% of the dose per g of body weight. By this time the activity in the soft tissues had largely cleared except for an appreciable amount in the large intestine. Excretion appeared to be through the intestines and kidneys. Skeletal uptake was 20-45% at 24 hours post injection, and there appeared to be proportionately higher skeletal uptake from smaller doses. When compared with IV injections of calcium [^{45}Ca] lactate, the distribution of strontium-89 appeared identical. Activity in soft tissue, liver and fat was negligible in comparison with that in bone.

Skeletal uptake of strontium-89 given as the chloride, lactate or gluconate salt were compared at 48 hours following IV or PO administration to mice. Within the IV and the PO groups there was no difference between the salts in skeletal uptake of strontium-89. Administration by the IV route gave approximately 33.4% skeletal uptake while the PO route gave 10.8% uptake. Large doses (2-8 mCi/kg) to mice resulted in leucopenia where average white cell counts fell from about 14×10^9 cells/L to 4.2×10^9 cells/L.

No histological change of normal bone structure was seen at 2 weeks after injection of 174 μCi or at 2 months after injection of 50 μCi of strontium-89. It is reported that rabbits also showed a leucopenia. This was not seen in mice or rabbits following non-radioactive strontium lactate given IV at 2360 mg/kg (mice) or 700 mg/kg (rabbits).

3.2.2 Mice

This was a paper by Stather, JW (1972) "Distribution Studies on ^{32}P , ^{45}Ca , ^{85}Sr and ^{133}Ba in the Mouse" in Second International Conference on Strontium Metabolism, Glasgow. Mice of the TO (Swiss) strain at 3, 8 or 26 weeks of age were injected IP with the chloride salt of the various radionuclides. Animals were sacrificed at 1 or 128 days post injection.

At 24 hours post injection the distributions of the various radionuclides were very similar. The skeletal accumulation of ^{85}Sr was about 90% of the total body activity, but for ^{32}P it was only about 40%. At 128 days post injection, activity in the various bones was more uniform but the percentage retention reflected the age of the mice at initial injection: retention of injected ^{85}Sr being 25% (3 week old at injection), 15% (8 week old) and 8% (26 week old). Initial distribution of ^{85}Sr correlated with the skeletal areas having a high proportion of trabecular bone (lumbar vertebrae) and less activity in cortical bone (radio-ulna). The radiation from the trabecular located isotope could explain the leucopenia in the high dose study above.

Anderson, JJB (in the same conference proceedings) reported similar age-related findings in various strains of pigs and in beagle dogs. Retention of strontium-85 in dogs at puberty was considered to approximate the human teenage period, whereas the data from the more slowly growing miniature pig was considered to approximate the human neonatal and infant periods.

3.2.3 Rats

Literature before 1956 was reviewed by Engstrom et al (1958) "Distribution of ^{90}Sr in the Skeleton" in: Bone and Radiostrontium (Wiley) pp 80-99. Young adult rats (115-170 g) were studied by whole body autoradiography after IP injection of 10 μCi strontium [^{90}Sr] nitrate.

Pairs of rats were sacrificed at various time intervals up to 128 days (4 months) post injection. It was reported that at 5 minutes, a significant proportion of strontium-90 had been taken up by the skeleton but the largest amount was still in the abdominal cavity. Activity was seen in the lungs but not in the heart. After one hour, the lung activity had cleared and very little activity was seen in the abdominal cavity although peak skeletal activity did not occur until six hours post injection. At this time activity in the urinary bladder was noted and a very high labelling of the rat incisors. The metaphysis growth zone showed more strontium uptake than the shaft of the long bones. Over the next 8 days there was a very small decrease of activity seen in the skeleton. In autoradio- graphs at days 16, 32 & 64 there was slight reduction reported in skeletal activity. Isotope labelling in the incisors gradually moved towards the apices in agreement with the known rate of continuous growth of rat incisors, which are "replaced" every 2 months. At 128 days, no change (ef day 64) could be detected, suggesting that the isotope retention was permanent after 2 months. Further studies in rats, dogs and rabbits emphasised the rapid and greater uptake by growing bone and by bone trabeculae and spongiform bone (less mineralised areas), and by callus formation around a bone break.

3.2.4 Rats

This was a paper by Weber, DA., Greenberg, EJ., Dimich, A et al (1969) "Kinetics of radionuclides used for bone studies." J Nucl Med 10: 8-17. This submitted paper did not mention strontium-89.

Rats and humans were injected IV with sodium fluoride [^{18}F], calcium [^{47}Ca] chloride, or strontium [^{85}Sr] nitrate. The nuclides were found to localise satisfactorily in bone lesions (fracture callus after 11 days in rats or cancer metastases in man). After waiting for about 5 hours (rats), excretion of background (non-lesion) activity allowed scans to detect the nuclides in the lesions at an higher ratio than in surrounding tissue. Consideration of kinetics showed fluorine-18 to localise in bone lesions most rapidly; and showed the most rapid plasma clearance; the highest lesion-to-normal bone differential; and decayed most rapidly.

3.2.5 Rats & Rabbits

This was a 1984 **Amersham** study (Report PS/134). Strontium-85, a gamma emitter, was used to simulate strontium-89, a beta emitter. Strontium-85 (salt not specified) was injected intravenously into rats and rabbits (strains not specified) at strontium single doses of 100-1400 $\mu\text{g/kg}$. All animals were sacrificed at 48 hours post injection and organs and tissues dissected and assayed. The laboratory accepted the usual assumptions for body content, being for rat: muscle (43%), blood (5.8%) and bone (5%) as percentages of total body weight; and for rabbit: muscle (56%), blood (4.25%), while a pair of rabbit femurs was taken to be 10% of total rabbit skeleton (ref stated).

At 2 days the rat retained 65% of the strontium-85 and no major organ contained significant amounts of the isotope except the bone which contained 49.3-60.4% of the injected dose. Rabbits showed wide variability but, at 2 days, 26.4-50.3% of the injected dose was estimated to be in the skeleton. The predominant route of excretion in the first 2 days was the urine.

However, faecal excretion in rats and rabbits reached 20% and 30% respectively of the total excretion. With the knowledge of the report at sect 3.2.7, it is disappointing that counts in bones other than the femur were not made.

3.2.6 Rabbits

This was a paper by Smith, H (1967) "Mechanism of citrate in influencing the excretion of radioactive strontium", In: Strontium Metabolism: Proceedings of The International Symposium. Edited by Lenihan, JMA et al (Academic Press) pages 323-328. Rabbits were injected intra-arterially with strontium-85 and an infusion of sodium citrate established at 2.2 mg/kg/minute to maintain a plasma citrate concentration of approximately 40 mg/mL over the 4.5 hours of study. A citrate/strontium complex formed in the plasma with increased urinary excretion over the first hour. This resulted in a compensatory smaller deposition in the skeleton, but did not significantly alter the body distribution of residual radioactivity. It did not affect the partitioning of strontium from plasma into erythrocytes. In the Control and Treated rabbits, the injected strontium was excreted via urine and the GIT. At the end of 4.5 hours, Control rabbits showed comparatively little deposition of strontium in soft tissues, heart & lungs, liver, kidneys or skin.

Rabbits: Distribution of injected strontium-85
(percentage of the dose)

	Controls	Citrate treated
Skeleton	86.5	75.4
Urine	3.5	13.8
GIT	9.2	7.9
Soft tissues	0.2	0.6
Heart & lungs	0.1	0.1
Liver	0.1	0.3
Kidneys	0.2	0.3
Skin	0.2	1.5

3.2.7 Rabbits

This was a paper by Subramanian et al (1972) Radiology 102: 701-704. The authors injected strontium-85 (salt not stated) intravenously into NZ Albino rabbits and sacrificed 6 animals at each time interval of 1, 3, 6 and 24 hours post injection. Careful dissection and replicate counting of multiple samples were carried out on tibia, femur, spine, pelvic bone and other tissues.

The authors reported the rabbit skeletal uptake of strontium-85 at the separate times to be 47.6% (1 hour), 62.0% (3 h), 49.2% (6 h) and 43.6% (24 h). It was noted that the uptake of isotope varied over the skeleton, with activity in the pelvis and spine being much higher than that in the femur and tibia. At 24 hours there was negligible activity in all other tissues. The cumulative urinary excretion was approximately 18% up to 3 hours post injection. Uptake of strontium-85

was studied 3 weeks after a tibial fracture in the rabbit, and the callus formation found to contain an higher content than the normal tibia at 2, 3, 12 and 24 hours post injection.

3.2.8 Rabbits

A paper by Kidman, B., Tutt, ML. & Vaughan, JM (1950) The retention and excretion of radioactive strontium and yttrium in the healthy rabbit. J Path Bact 62:209 showed that the calcium content of the diet affected the retention of strontium measured over 9 days after a strontium-89 injection. In 6-month old rabbits on a medium calcium diet there was a retention of 17.1% of the strontium dose. Values in animals on low and high calcium diets were 57.1% and 11.7% respectively. This might have relevance for efficacy in human use.

3.2.9 Distribution in pregnant mice

Paper by Jacobsen, N., Alfheim, I. & Jonsen, J (1978) Nickel and strontium distribution in some mouse tissues: Passage through placenta and mammary glands. Res Commun Chem Pathol Pharmacol 20: 571-584. Adult female mice were injected IP with nickel [⁶³Ni] chloride or strontium [⁸⁹Sr] chloride. The authors reported that the acid soluble part of the bones showed a strontium concentration 100-1000 times that of the soft tissues. Progeny receiving strontium through the placenta or the mammary glands showed a distribution pattern similar to that of their mother, with retention of strontium in mineralised tissue.

3.3 Kinetics

3.3.1 Monkeys

The following statement was taken from the review by Engstrom et al (1958) "Distribution of ⁹⁰Sr in the Skeleton" in: Bone and Radiostrontium (Wiley) pp 80-99.

"In rhesus monkeys, average half-times for skeletal retention of strontium-90 were calculated for an adult male as 470 days, and for an adult female who had experienced three closely spaced pregnancies as 315 days."

Therefore, if strontium-89 behaved similarly, most of the skeletal retained isotope will remain in place while it decays to negligible activity.

3.4 Excretion

3.4.1 Mice, rats, rabbits

Excretion of radiostrontium in various species was reviewed by Engstrom, A., Bjornerstedt, R., Clemenson, CJ. & Nelson, A. (1958) "The problem of internal radiation hazards from radiostrontium" in: Bone and Radiostrontium (Wiley) pages 9-27.

"After a parenteral injection of radiostrontium, maximum excretion will occur in the first two days in all species. Thereafter the elimination decreases to an extremely low level. In the case of strontium-89 the excretion after the first two weeks is less than the rate of physical decay of the isotope."

The following values for the average total excretion are in per cent of the administered dose:

mouse	54%
rat	40%
rabbit	70%

Age and diet had less effect on faecal than on urinary excretion of strontium-89 and strontium-90 in rabbits. The elimination by both routes was less on a low than on a high calcium content diet. If calcium content was low, faecal excretion always exceeded the urinary one. In general, the excretion through either route was greater in rabbits aged 6 months than in those 5-7 weeks old. In mice, there was a greater excretion of strontium in faeces than in the urine. Adult rhesus monkeys eliminated 56% of IV injected strontium-90 in the urine during the first 10 days after injection.

3.4.2 Rats

This was a paper by Thompson, RC & Hackett, PL (1967) "Urinary/faecal excretion ratios of strontium and calcium in the rat" in: Strontium Metabolism: Proceedings of an International Symposium, eds: Lenihan JMA et al (Academic Press) pages 255-260.

Sprague-Dawley female 10-month old rats of 380 g body weight on a high calcium diet were injected IP with strontium-85 (30 μ Ci) or calcium-45 (60 μ Ci). There was no adverse effect on weight gain, food consumption, urine volume or faeces weights over the test period of 50 days.

Over the first 30 days, daily urinary excretion of strontium-85 exceeded its faecal excretion. After about day 30, faecal excretion of strontium-85 exceeded its urinary excretion. Excretion clearances were estimated at days 7 and 47 when the intestinal clearance of strontium-85 was found to have increased nearly five-fold, while renal clearance appeared unchanged. The authors suggest that as the study progressed the remodelling process in the bone may have removed strontium in a form more amenable to excretion via bile and intestines.

3.4.3 Rats

One submitted paper investigated whether various compounds administered orally affected the excretion of freshly administered strontium-85 to rats. It was seen that phosphates increased the faecal excretion of strontium at the expense of its urinary excretion. Sulphates increased the accumulation of strontium in the small intestines, but later, appeared to increase its urinary excretion. Absorbable alkaline earth chlorides given orally to the rats before the injection of strontium-85 appeared to increase the excretion of strontium. The study did not investigate the situation where strontium had already located in the skeleton.

4.0 ACUTE TOXICITY

4.1 Non-radioactive strontium

4.1.1 Mice

Paper by Syed, IB & Hosain, F (1972) Tox Appl Pharmacol 2: 150-152 estimated the acute toxicity (in ICR strain mice) of each of the following chlorides and revealed strontium ion to be the least toxic:

Intravenous LD₅₀ mg/kg mEq/kg
(Values for the ion although injected as the chloride)

strontium	147.6	3.36
calcium	42.4	2.12
barium	19.2	0.28
magnesium	14.4	1.18

Deaths usually occurred rapidly following IV injection and there were no delayed deaths. Signs reported with strontium were violent struggling, sinus bradycardia and great difficulty in breathing, with death from respiratory failure. Death with calcium appeared to be from cardiac failure.

4.1.2 Mice and Rats

The acute toxicity of non-radioactive strontium chloride has been published by various authors. The following tabulation was collated by Sax NI & Irving RJ (1989) Dangerous Properties of Industrial Materials 7th Ed (New York: Van Nostrand Reinhold) Vol 3, pp 3121-3124:

Strontium ion LD₅₀ mg/kg (and as chloride)

Route	Mice	Rats
IV	148 (267)	123 (222)
IP	908 (1643)	224 (405)
PO	1714 (3100)	1244 (2250)

4.2 Strontium-89 single dose toxicity

The following statements on mice and rats were taken from the review by Engstrom, A., Bjornerstedt, R., Clemenson, C.J., & Nelson, A. (1958) "The problem of internal radiation hazards from radiostrontium" in: Bone and Radiostrontium (Wiley) pages 9-27.

4.2.1 Mice

"The LD₅₀ at 30 days for strontium-89 in young mice was found to be 8 mCi/kg body weight. Forty nine per cent (49%) of the animals which had received 5 mCi/kg and which had survived for 200 days, died before 250 days. Fourteen per cent (14%) of these animals had developed bone tumours."

4.2.2 Rats

"It was found that a single IP injection of strontium-89 at slightly less than 5 mCi/kg body weight to adult rats produced 50% mortality in 30 days. Also 2.9 mCi/kg body weight was lethal in two weeks in 95% of 50 g rats."

4.2.3 Mice

Paper by Rozing, J., Buurman, W.A. & Benner, R (1976) Cellular Immunology 24: 79-89. The authors demonstrated that an injection of strontium [⁸⁹Sr] chloride (Amersham) IV or IP to hybrid C57BL x CBA F1 mice caused a dose related bone marrow aplasia. A dose of 3 mCi/kg resulted in about 2.8% of cells remaining in the bone marrow at 14 days post injection. This dose also resulted in a virtual absence of B-cells in the bone marrow after 7 days. In the spleen there was a drop in the total number of nucleated cells and, after 3 days, was followed by a recovery up to normal values.

4.2.4 Mice

Paper by Bennett, M., Baker, E.E., Eastcott, J.W., Kumar, V. & Yonkosky, D (1976) Selective elimination of marrow precursors with the bone-seeking isotope ⁸⁹Sr. J Reticuloendothelial Soc 20:71-87. Mice of the C57BL/6 strain were injected IV with 100 µCi of strontium-89 (salt not stated) and a second injection after one month interval. (If the mice were about 33 g body weight, then the dose is in the order of 3 mCi/kg).

"In the treated mice the bone marrow became hypoplastic containing mature granulocytes and erythrocytes. Spleens were enlarged to a variable degree and the red pulp was extremely active with myelopoiesis. This activity reflecting the fact that the spleen had taken over all stem cell functions of the mouse. The white pulp was much less conspicuous than the red pulp but was not hypoplastic and occasional follicles with germinal centres could be identified. Thymus and lymph nodes appeared normal except for the occasional finding of foci of granulopoiesis. There was a moderate to extensive infiltration of lymphoid tissue with mast cells."

The authors reported that most of the tested functions of the T-cell, B-cell and macrophages were normal in the treated mice. But the animals lost the resistance to marrow and lymph node allografts and showed increased susceptibility to infection with Friend leukaemia virus and *Listeria monocytogenes*.

4.3 Strontium-90 single dose toxicity

The following statements on mice and rats were taken from the review by Engstrom, A., Bjornerstedt, R., Clemenson, C.J., & Nelson, A. (1958) "The problem of internal radiation hazards from radiostrontium" in: *Bone and Radiostrontium* (Wiley) pages 9-27.

4.3.1 Mice, rats, dogs, monkeys

"The LD₅₀ at 30 days for mice was 6 mCi/kg body weight, and for dogs an LD₅₀ at 30 days of 0.15 mCi/kg. In monkeys a single injection of 0.2 mCi/kg has been proven to be fatal.

A single IP injection of strontium-90 in 4-6 week old male Long-Evans rats gave an LD₅₀ at 50 days of 2.5-3.0 mCi/kg.

A similar value of slightly less than 2.5 mCi/kg was found for rats of the Sprague-Dawley strain."

4.3.2 Rabbits

Paper by Vaughan, J. & Williamson, M. (1967) "Variation in turnover rates in different parts of the skeleton in relation to tumour incidence due to strontium-90 deposition" in: *Proceedings of the First International Symposium on Strontium Metabolism* (Academic Press) pages 195-206.

In previous strontium-90 studies in rabbits, the authors found that the site of induced tumours varied with age at treatment. Rabbits that were 0-8 weeks old at treatment produced carcinomas of the "ear bone" (described as the petrous temporal bone enclosing the external, middle and inner ear). Those that were 6-8 weeks old also produced osteosarcomas of the diaphysis of the long bones. Those that were 6-8 weeks, but given larger doses, died within six months of treatment and all showed osteosarcomas of long bone metaphyses and of the jaw. Those that were 52 weeks of age at treatment and given a large dose showed osteosarcomas of the jaw only.

The paper under review reported that strontium-90 was injected IP as 500 μ Ci/kg to 2-day old rabbits; 50 or 100 μ Ci/kg to 6-week old rabbits; and as 600 μ Ci/kg to other 6-week old rabbits.

In the 2-day old group, the strontium localised in the ear bone and throughout the long bones. Over the 9-month period of autoradiographs, radioactivity decreased throughout the long bones as a result of normal remodelling, but not in the ear bone. The deposition in the ear bone with its lack of turnover correlates with the tumour occurrence in this very young group.

The 6-week old rabbits that received the smaller dose of strontium-90 showed pronounced uptake in the metaphyses with uptake also in the shaft of the long bones. Nine days later, remodelling moved the strontium from the metaphyses but not from the shaft where it was still pronounced at 6-months, and would explain the osteosarcomas at this site.

The 6-week old rabbits that received the larger dose (600 $\mu\text{Ci/kg}$) of strontium-90 showed pronounced retention of the radionuclide in the metaphyses at 30 days post treatment. The osteosarcomas that developed in the metaphyses are explained by the authors as an high uptake at 6 weeks of age causing damage to the resorption and remodelling process so little strontium-90 was lost from this site.

5.0 REPEAT DOSE TOXICITY

Submitted studies did not have GLP certification.

5.1 Non-radioactive strontium: Pigs

The following statement was taken from page 47 of Clinical Toxicity of Commercial Products edited by Gosselin, RE., Hodge, HC., Smith, RP & Gleason, MN (Williams & Wilkins) 4th Ed 1976:

"On a chronic diet high in strontium and low in calcium (ratio 3.1), young pigs developed severe bone deformities, incoordination, weakness and hind leg paralysis."

It is not clear whether the toxicity was a result of the high amount of strontium (amount not stated), or of the low calcium (amount not stated), or of the combination of both factors.

5.2 Strontium-89: Rats

Paper by Kuzma, JF. & Zander, G (1957) Cancerogenic effects of Ca^{45} and Sr^{89} in Sprague-Dawley rats. A.M.A. Arch Pathol 63: 198-206. Female Sprague-Dawley rats of about 3.5 months of age were injected IP with calcium-45 or strontium-89 daily for 10 days or with the same doses monthly for 10 months. The repetitive doses were 0.01, 0.05, 0.10, 0.25 or 0.35 mCi/kg body weight.

Rats administered 0.35 and 0.25 mCi/kg daily died within 6 and 9 months respectively. The authors considered the cause of death to be a result of bone marrow destruction.

Rats that received daily dosing at 0.05 and 0.1 mCi/kg or monthly dosing at 0.25 and 0.35 mCi/kg developed malignant tumours (chiefly osteogenic sarcomas in the hind legs) with the lungs being the most common site of metastases. The latent period to detection of a bone tumour was 6.5 to 8.5 months, and strongly dose related. The results for calcium-45 were similar but less marked. No bone tumours were detected in untreated Controls; or in rats of the lowest daily dose group; nor in the monthly strontium-89 dose groups of 0.01, 0.05 and 0.10 mCi/kg. Fractures occurred in some strontium-89 treated rats but only in tumour affected bones.

An unexpected finding was the tumour occurrence in the soft tissue of the snout in seven rats injected with strontium-89. These were described as squamous cell carcinomas developed from the mucosa.

Explanation of this localisation was not apparent.

6.0 CARCINOGENICITY

In sections 4.2.1 & 5.2 strontium-89 was reported to have caused bone tumours in mice and rats, and in section 4.3.2 that strontium-90 had caused bone tumours in rabbits. The results indicate that a radionuclide may present a risk of carcinogenesis if it localises at a site of slow turnover, and that a large dose may present a risk at a site of high turnover if it damages and reduces the turnover process. In the study above (Sect 5.2), rats developed bone tumours within about 8 months after 10 daily injections of strontium-89 at as little as 0.05 mCi/kg (total dose of 0.5 mCi/kg). This dose is only about 9 times larger than the proposed clinical dose. The review by Engstrom, A., Bjornerstedt, R., Clemenson, C.J., & Nelson, A., (1958) "The problem of internal radiation hazards from radiostrontium" in: Bone and Radiostrontium pages 9-27, further reviewed the carcinogenic dose of strontium-89 in mice and rats, finding it to be 0.7-1.6 mCi/kg. Although having a shorter physical half-life than strontium-90 (a known bone carcinogen), strontium-89 emits β^- electrons of nearly three times the energy of strontium-90 (1.463 MeV compared with 0.546 MeV of strontium-90). Strontium-89 must be considered to pose a risk of causing bone tumours in humans. However, the benefit may be considered to outweigh the risk in patients needing pain relief from bone metastases during terminal stages of cancer. Young animals, because of their actively growing bones, appeared to be at high risk of bone tumours caused by radiostrontium. Children, with their potentially longer life span, should be excluded from therapy with strontium-89 unless alternative therapy was unsuccessful.

The carcinogenic risk may need to be stated as part of the benefit-to-risk estimation before its use.

7.0 GENETIC TOXICITY

No data submitted under this heading. Strontium-89 would be expected to be mutagenic and to cause chromosomal aberrations in vivo by means of its beta radiation. This may need to be stated as a part of the benefit-to-risk estimation before its use.

8.0 REPRODUCTIVE TOXICITY

No data submitted under this heading. Strontium-89 is known to cross the placenta and deposit in the fetal skeleton. Strontium-89 may be expected to cause fetal bone marrow damage and initiate fetal bone tumours. Although the product is not intended for use in women in Australia, overseas usage and trials are for bone metastases secondary to breast cancer. As these reports may encourage such use here, a warning against its use in pregnancy should be included in the PI.

REPLACEMENT PAGE 17

It is recommended that the categorisation of risk of drug use in pregnancy for strontium [^{89}Sr] chloride should be Category D.

Strontium-89 is known to pass into milk. Therefore the PI should warn against the use of strontium [^{89}Sr] chloride in nursing mothers.

8.1 Use in Pregnancy

The following warning is suggested for the Australian PI:

"Categorisation of risk of drug use in pregnancy is Category D.

Strontium [^{89}Sr] chloride (METASTRON) is not to be administered to pregnant women or nursing mothers."

XXXXXXXXXXXXXXXXXXXXX

Drug Evaluation Branch

27-4-92.