REPORT

IRSN
INSTITUT
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Evaluation of the use of pectin in children living in regions contaminated by caesium

State of the art and critical analysis of publications

RADIOLOGICAL PROTECTION AND HUMAN HEALTH DIVISION

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Introduction

In a letter addressed to Mr. Jacques Repussard, Director General of the IRSN (French Institute for Radiological Protection and Nuclear Safety) dated the 28 April 2005, Mr Stéphane Chmelewsky, the French Ambassador to the Republic of Belarus, approached the IRSN in order to initiate a pluralist evaluation of the efficacy of pectin and the opportuneness of its use in regions contaminated by radioactive fallout following the explosion of reactor N°4 of the Chernobyl nuclear power plant.

This request lies within the framework of a presentation made at a meeting of the CORE Programme Approval Committee by Professor Vassili Nesterenko, member of the National Academy of Sciences of Belarus, of a project in which the use of pectin formed an important part. When examining this project, important divergences of opinions became apparent within the Committee on the role that the use of pectin could play in reducing contamination levels in children living in regions affected by the fallout.

The approach adopted by the IRSN consisted, firstly, in carrying out a critical bibliographic analysis of the scientific and technical arguments put forward until now with regard to pectin in order to clearly identify the points of controversy and any gaps in our knowledge with regard to its use as a food additive in regions contaminated by caesium. Moreover, in order to have at our disposal a coherent set of data, this analysis focused not only on the role of pectin on caesium, but also its other uses in humans.

The scientific basis on which the bibliographic analysis undertaken is based was constituted from a search carried out by means of the principal search engines and data bases used by the international scientific community (Academic Search Premier, Biosis, Embase, ISI, Medline, Pub Med, Science Direct, Scirus, Scopus and Springer Link). This search has enabled 48 documents to be selected. Moreover, with an aim to completeness, we included in the dossier reports not published in international scientific reviews but which have a specific interest, certain of which disclose recommendations made by the Russian and Belarusian ministries responsible for public health. Finally, it should be pointed out that all of the documents handed over by Professor Vassili Nesterenko to the French Ambassador to the Republic of Belarus were also analysed.

This report comprises 4 sections:

- The first part summarises current knowledge of the biological and medical effects of pectin in human nutrition and in the event of exposure to heavy metals.

- The second part presents a critical analysis of publications relating to the biological and medical effects of pectin in the event of chronic incorporation of radionuclides. In order to take a critical look at the methodology employed and the pertinence of the conclusions presented by the authors, the documents were analysed as they would be by the assessors of the editorial committees of international scientific reviews. Moreover, we made a distinction between articles published in scientific reviews (§ 2.1), documents not published in scientific reviews but that give the results of experimental work (§ 2.2) and finally, synthesis reports not published in scientific reviews and that do not give the results of experimental work (§ 2.3).

- The third part is a synthesis that highlights the principal lessons learned from this bibliographic analysis.

- The fourth part presents the proposals of the IRSN with regard to future work and studies that should be undertaken in order to complete our knowledge with regard to the use of pectin in the event of chronic incorporation of radionuclides.

Thus, the synthesis performed by the IRSN is based on a total of 54 documents, 10 of which are in Russian. These Russian documents were translated into English and the translations were systematically checked by a second translator of Russian nationality. The references of the documents analysed are given at the end of this report, with those that were translated from Russian into English marked with the following notation [Article in Russian].

1. State of the art with regard to the biological and medical effects of pectin in human nutrition and in the event of exposure to heavy metals

1.1 Structure and origin of pectin

Pectin is a polymer of galacturonic acid that is principally found in the cell walls of plants. It can be extracted from fruit pips, the pulp and the peel of apples, sugar beet, sunflower and even seaweed. It is a branched anionic polysaccharide, the molecular weight of which can vary from 50 to 150 kilodaltons. The backbone of pectin is mainly composed of D-galacturonic acid units linked together by α-(1$\rightarrow$4) glycosidic bonds (figure 1).

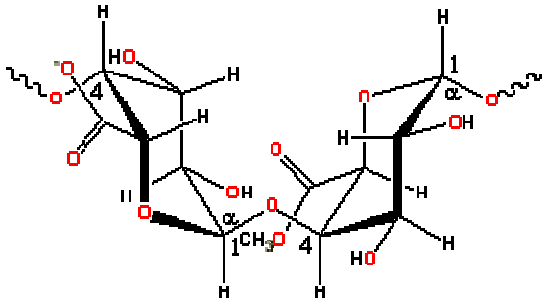

Figure 1: Unit structure of pectin backbone

Pectin can have different levels of esterification; this is quantified by the percentage of carboxylic groups esterified by a molecule of methanol. Thus, three categories of pectin may be distinguished [23]:

- The pectin is known as high methoxyl pectin when the degree of esterification is greater than 50 %.

- The pectin is known as low methoxyl pectin when the degree of esterification is below 50 %.

- The pectin is known as pectic acid when the degree of esterification is below 10 %.

From a metabolic viewpoint, since pectin is not degraded by the intestinal enzymes when it passes through the stomach and the small intestine, it is present in macromolecular form throughout the length of the intestine [15]. Unlike cellulose, the other principal component of plant cell walls, pectin is intensively degraded at the level of the colon [16,45].

The hydrophilic and anionic character of pectin in solution has led it to be proposed, in the same way as alginates or cellulose, as an intestinal absorbent, the non-esterified carboxylic functions being able to form complexes with cations such as calcium, magnesium or iron, thus preventing their digestive resorption. Moreover, it is used in the food processing industry as a gelifier, thickener, stabiliser or emulsifier additive. Finally, it is used in the formulation of pharmaceutical specialities for its anti-acid (GELOPECTOSE®), hemostatic (ARHEMAPECTIN ANTIHEMORRAGIQUE®) or anti-diarrhoea (TANALONE®) properties.

1.2 Use of pectin in human nutrition

By virtue of its intrinsic physical and chemical properties, pectin can play a beneficial role in human nutrition by trapping a certain number of elements present in the intestinal lumen, such as bile acids. For example, its interactions with the lipidic metabolism have been recognised for several years. Indeed, bile acids are capable of linking to pectin by bringing into play bonding or adsorption mechanisms [20,32], thus contributing to increasing the pool of excreted bile acids, the principal consequence of which is a reduction in the bile acid pool present in the body. This imbalance between the pools present and excreted thereby results in an increase in the synthesis of bile acids

and a reduction in hepatic cholesterol, very probably behind **the reduction in the serum levels of cholesterol** observed in cases where pectin has been administered [22,35].

Moreover, **a reduction in the intestinal absorption of amino acids, sugars (such as glucose) and sodium and chloride ions** following an oral administration of pectin has also been observed [17,30,47,48]. These effects may be attributed to an increase in the unmixed boundary layer present on the mucosal surface [21]. The structure of pectin administered seems to have an influence on these intestinal absorption modifications: thus, high methoxyl pectins have a more pronounced inhibitor effect on glucose absorption than low methoxyl pectins [30]. However, these results run counter to those obtained by Chun and coll., which indicate a hyperplasia of the intestinal mucous and an increase in the enzymatic activities of the membranes of the brush border [11].

Thus, the properties of pectin result in **a general increase in the excretion of molecules present in the gastrointestinal tract.** The effects of ingestion of pectin may therefore not only be beneficial (metals, radionuclides) but also deleterious (minerals, vitamins) depending on the elements in question.

1.2.1 Effects of pectin on the bioavailability of minerals

It is now well known that the beneficial effects of dietary plant fibres should not mask their undesirable effects on the biological availability of certain nutriments, particularly minerals and vitamins. Rachitogenic effects were first highlighted in 1921 in humans and dogs fed a diet rich in whole grain cereals [34]. Multiple deficiencies in minerals, particularly zinc, have thus been observed in rural populations that eat unleavened bread [38]. The inhibitor effect of cereals on these minerals, initially attributed to the presence of phytic acid, was extended to pectins as of 1978 [26]. In pigs, a diet of apple pectin in quantities above 2.5 % leads to the onset of diarrhoea [26]. Disorders of the gastrointestinal tract were also observed in rats fed low esterified apple pectin [9].

The effects on minerals depend on the degree of esterification and the type of pectin administered [18]: thus, a low methoxyl pectin reduces the absorption and the retention of minerals, and then leads to an imbalance in the calcium, magnesium and zinc elemental balance. This effect of pectin results in a reduction in the bioavailability of these elements, as has been demonstrated for Zn^{2+} [53]. Moreover, the results of certain studies suggest an additional effect of pectin on the resorption of endogenous cations in the intestine. These studies therefore highlight **a harmful effect of low esterified apple pectin on the minerals balance, particularly calcic minerals.** In conclusion, **the authors of these studies advise against the use of low esterified pectins in human nutrition.**

Table I summarises data from the literature relating to the effects of pectin on the bioavailability of minerals. It appears that **the administration of pectin may lead to a reduction in the bioavailability of monovalent and divalent minerals for the body, which may have as a consequence a nutritional deficit in minerals.** This conclusion must however be modulated as a function of the type of pectin, particularly its degree of esterification.

Table I: Effects of pectin on mineral bioavailability

MINERALS

Type of pectin	Posology	Length of treatment	Model	Effects	Reference
Apple pectin	10 g	2 hours	*In vitro*	↓ Zn availability = Ca availability = Fe availability	Van Dick, 1996 [53]
Lemon pectin	80 g/kg food	9 days	Rats	↑ Fe availability	Kim, 1996 [30]
Apple pectin	2.5 %	10 days	Pigs	High HM: = absorption and retention of P, Ca, Mg and Zn Low HM: ↓ absorption of P, Ca, Mg and Zn	Bagheri, 1985 [1]
Lemon pectin	2 %	4 weeks	Rats	= Fe turnover and absorption	Baig, 1983 [2]
Lemon pectin	2.5 %	6 weeks	Rats	↓ K, Na, Zn, Cu, Ca, Fe, Mg serum levels	El-Zoghbi, 2001 [18]
Pectin	36 g/day	6 weeks	Humans	= Ca balance	Cummings, 1979 [13]

HM: high methoxyl ; LM, low methoxyl

1.2.2 Effects of pectin on the bioavailability of vitamins

Several studies have researched the possible deleterious effects of pectin on the intestinal absorption of vitamins. The first studies were devoted to determining the effects of diets rich in fibres on the bioavailability of vitamin A [28,29], vitamin B12 [12], vitamin B9 [40] and vitamin E [46]. One study reports an **increase in serum levels of vitamin A, if this is given jointly with apple pectin** [26]. Conversely, another study highlights a reduction in the serum levels of vitamin A after ingestion of dietary plant fibres [29]. **The ingestion of pectin leads to a depletion in vitamins B12,** probably *via* a effect on the enterohepatic cycle [12], **and a reduction in the bioavailability of vitamin E** [46], but not vitamin B9 [40].

As has been pointed out above, the effects of apple pectin need to be modulated as a function of the nature of this pectin [19]. Nevertheless, **the results of these studies go in the sense of a reduction in the bioavailability of vitamins, which can lead to important deficits in the case of chronic use of dietary plant fibres.**

Finally, it is worth underlining the absence of scientific publications on the interaction of dietary fibres and vitamins over the last 15 years. It is probable that the deleterious effects of dietary plant fibres on the bioavailability of vitamins (and minerals) have stifled interest in these food components in human nutrition.

All of the data analysed with regard to the effects of pectin on the bioavailability of vitamins is summarised in table II. **The synthesis of these studies clearly shows a reduction in the bioavailability of vitamins for the body.** Vitamin nutritional deficiencies could therefore be observed over the more or less long term in the event of chronic administration of pectin. **The use of pectin would then require a nutritional supplement, particularly of vitamins.**

Table II: Effects of pectin on vitamin bioavailability

VITAMINS

Type of pectin	Posology	Length of treatment	Model	Effects	Reference
Apple pectin	15 g	Unique	Men	↑ Vitamine A serum levels	Kasper, 1979 [28]
Mixture of dietary fibres		5 weeks	Rats	↓ Vitamine A serum levels	Khokhar, 1990 [29]
Pectin	5 %	19 days	Rats	Depletion vitamine B12	Cullen, 1989 [12]
Pectin	3, 6, 8 %	8 weeks	Rat	↓ Vitamine E availability (pectin >6 %)	Schaus, 1985 [46]
Pectin Lignin Alginate	3 %		*In vitro* Chickens	= Vitamine B9 availability	Ristow, 1982 [40]
Lemon pectin	7 %	4 weeks	Chickens	↓ Beta-carotene availability	Erdman, 1986 [19]
Lemon pectin	150 mg/kg bodyweight	Unique	Women	↓ Beta-carotene, lycopene, lutein availability	Riedl, 1999 [39]

1.3 Effects of pectin in the event of exposure to heavy metals

Experiments on the use of pectin as a substance enabling the elimination of radionuclides and heavy metals in animals and in humans first began in 1977 [24,41,49].

Several studies have reported the use of dietary plant fibres such as pectin as a decorporating agent in experimental models of lead, cadmium or mercury poisoning [24,31,33,42,43,54]. **These studies do not show in a unanimous manner a beneficial effect of dietary plant fibres on the reduction in the retention of heavy metals within the body.** Certain results are contradictory, probably as a result of the experimental conditions, the composition and/or the posology of the diet (nature of the dietary plant fibres), and as a function of the metal considered. Consequently, **no study has really highlighted any significant reducing effect of pectin on cadmium tissue levels** [31,42]. **The addition of pectin associated with kaolin does not provide any benefit in terms of absorption and urinary excretion of lead** [54]. In the same way, **the use of pectin does not modify in a significant manner the tissue and blood levels of mercury,** whereas the ingestion of wheat bran or the husks of sunflower seeds appears to efficaciously reduce the tissue levels of mercury [33,43]. The authors put forward the hypothesis that it is the lignin component of the bran that binds to the metallic ions [43]. It should however be noted that experiments conducted on rats show **a prophylactic effect of apple pectin in the case of lead intoxication** [9].

A study carried out *in vitro* has shown moreover that **beet pectin has a high affinity for the ions Pb^{2+} and Cu^{2+}, apple pectin for the ions Co^{2+} and lemon pectin for the ions Ni^{2+}** [27]. In this study, the authors demonstrate the very weak bonding properties of pectin with the ions Cd^{2+}, which is in agreement with the studies showing that the ingestion of pectin has no significant effect on the tissue levels of cadmium. Similar results have been obtained by other authors who have shown that the bonding of cadmium with dietary plant fibres is variable, depending on the nature of the fibres [31]. In an interesting manner, the dietary plant fibres that have the strongest bond with cadmium (lignin and Na-carboxymethylcellulose) are those that have the most pronounced inhibitor effect on the intestinal absorption of cadmium.

In parallel, studies on humans have been carried out on the prophylactic use of pectin for workers exposed to mercury or lead [14,50,52]. Daily ingestion over a period of several weeks of a

preparation based on several active substances (PVP or Pectin Vitamin Preparation, a complex containing, in particular, cellulose, pectins and vitamins) makes it possible to reduce the blood lead content and to improve the plasmatic parameters traditionally altered during exposure to lead [41,49]. These results bear witness to **the efficacy of this treatment in the case of chronic lead contamination** [50]. A similar efficacy has also been observed in children living in an environment contaminated by a large number of toxic substances (lead, arsenic, copper, chrome and cadmium) [14]. However, the use of a mixture comprising several active natural substances **does not enable a distinction to be made between the respective efficacy of each of the substances entering into the composition of the administered mixture.**

In conclusion, the analysis of the work carried out on **the use of dietary plant fibres to enable the decorporation of heavy metals only highlights pronounced beneficial effects of these fibres in the case of exposure to lead** (Table III). Possible beneficial effects with regard to other metals such as cadmium are more controversial. Moreover, in order to be able to make a definitive judgement on the efficacy of pectin within the framework of providing treatment after exposure to heavy metals, studies will have to be carried out by conducting administrations of pectin alone.

Table III: Effects of pectin in the event of exposure to heavy metals

HEAVY METALS

Type of pectin	Posology	Length of treatment	Model	Effects	Reference
Pectin	10 g/L	24 hours	*In vitro*	Bonding with Cd and Pb	Rose, 1987 [42]
Beet pectin Apple pectin Lemon pectin	5 g/L	4 hours	*In vitro*	High affinity for Pb High affinity for Co High affinity for Ni Pectins: Very low affinity for Zn and Cd	Kartel, 1999 [27]
Pectin	40 g/kg food	4 weeks	Rats	↑ Cd retention = Pb retention	Rose, 1987 [42]
Apple pectin	6 mg/day	6 weeks	Rats	Effect on Pb for 32 % esterified pectin	Bondarev, 1979 [9]
PVP	3-4 g/day	4 weeks	Workers	↓ Pb in urine	Trakhtenberg, 1995 [50]
PVP		3-4 weeks	Children	↓ Pb in blood	Degtiareva , 2001 [14]
Phytosorbent	10 g	12 days	Rabbits	↓ Hg in tissues	Lapina, 2000 [33]
Lemon pectin	2.5 %	6 weeks	Rats	↓ taux sérique Pb et Cd	El-Zoghbi, 2001 [18]
Pectin	1 %	6 semaines	Rats	↓ Pb toxicity = Pb absorption = Pb urinary excretion	Wapnir, 1980 [54]
Lemon pectin	133 mg/kg	7 days	Rats	= Cd tissue levels	Kiyozumi, 1982 [31]
Pectin	50 g/kg	3 months	Mice	= Hg elimination = Hg tissue levels	Rowland, 1986 [43]

2. Biological and medical effects of pectin in the event of chronic incorporation of radionuclides: critical analysis of publications

As described in the introduction to this report, this section presents a critical analysis of each of the documents while striving to summarise each document and to make comments as to the methodology employed and the conclusions drawn by the authors. In each of the 3 paragraphs of this chapter, the documents analysed are presented in their chronological order of publication.

2.1 Analysis of articles published in scientific reviews

1st article (1991) - Further improvement in the administration of pectin as a preventive agent against absorption of radionuclides by human body.
Romanenko AYe, Derevyago IB, Litenko VA, Obodovich AN.
Gig Tr Prof Zabol 12:8-10 (1991). [Article in Russian] [Reference 41].

Summary

In this article, the authors describe experiments carried out in order to evaluate the therapeutic potential of a **preparation based on pectin and vitamins (PVP)** obtained from the recycling of citrus fruit leftovers, **vitamin P, vitamins of the B group** (B_1 and B_2), **vitamin PP** (a mixture of nicotinic acid and nicotinamide), and **vitamin C** (ascorbic acid, dehydroascorbic acid). The efficacy of this product was assessed experimentally on ^{85}Sr and ^{137}Cs. The experiment was conducted on 30 female albino rats divided into two groups of 15. The first group was given a conventional diet (control group), whereas the other group was given the same dietary plan supplemented with 350 mg of PVP. After one week of adaptation of the animals to the dietary plan, radionuclides were introduced into the rats' food for 30 days until a body burden of 1306 Bq of ^{85}Sr/animal and 343 Bq of ^{137}Cs/animal was obtained. The radionuclide contents incorporated in the animals were determined by gamma spectrometry (Ortec unit, NaI scintillation detector, Bicron™, USA) every 3 days.

After **30 days** of experimentation, the animals did not show any signs of abnormalities in their health and the **PVP** (350 mg/animal/day) enabled a significant reduction in the accumulation of **^{85}Sr (-56.6 %)** and **^{137}Cs (-27.6 %)** in the body compared to the control group ($p<0.05$). The results are also compared with those obtained in previous studies carried out with **pure citrus pectin** or with **sodium alginate**: they shown that **PVP is around twice as efficient as pectin administered alone** and that it has an **efficacy comparable to sodium alginate for ^{85}Sr**. In the case of **^{137}Cs**, **PVP is around 1.5 times more efficacious than the other substances**. The authors conclude that the consumption of this food supplement PVP may enable a significant reduction in the intestinal absorption of strontium and caesium present in foodstuffs; the authors recommend a daily dosage of 4 to 6 grammes of PVP.

Analysis

This study has the merit of proposing a product composed of substances commonly used in foodstuffs (citrus pectin) or used as adjuvants (cellulose) and food supplements (vitamins). The importance of additives (cellulose, vitamins) in the "PVP" mixture in boosting the efficacy of pectin seems to have been demonstrated. **However, the authors do not make it clear if the absolute quantity of pure pectin administered is equivalent to that used in the previous studies.** Moreover, at equivalent dose in absorbent agents (pectin + cellulose), **the complex PVP mixture does not seem to present an additional interest in terms of efficacy of absorption of radionuclides compared to the pure alginate,** which, for its part, is already well known for these properties.

The experimental protocol is relatively satisfactory for evaluating the chelating effect in the gastrointestinal tract, both on ^{85}Sr and on ^{137}Cs. However, **the study does not allow one to estimate the subsidiary effect looked for and announced by the authors, namely an actual "decorporating" effect.** Moreover, since the PVP was administered at the same time as the contaminated foodstuffs, **this study does not provide any information that enables its preventive efficacy outside of a contaminated diet to be assessed.** Consequently, **these studies only**

evaluate the blocking power of PVP on the intestinal absorption of radionuclides but do not provide any information as to its ability to decorporate radionuclides previously incorporated in the body. To do this, it would have been necessary to contaminate the animals beforehand, take a measurement of their level of contamination in order to have a zero point, then reiterate these measures after administration of the PVP.

Furthermore, the mode of contamination of foodstuffs by caesium 137 or strontium 85 is not detailed, which means **it is not possible to take into account possible phenomena of complexation of these radionuclides with the intrinsic components of the food administered.** Indeed, the same does not hold true as to the bioavailability of radionuclides if the radionuclides are incorporated according to an incubatory mode (foodstuffs brought into contact with an aqueous solution of radionuclides) or if the foodstuffs have been contaminated under real conditions, in other words obtained from culture planning practiced on soil contaminated by radionuclides.

Moreover, statistical tests have not been defined and the sampling (15 rats per group) suggests that a Student test was used and that the authors considered a "normal" distribution of averages in order to be able to compare the groups between each other

Finally, **the comparison of the efficacy of PVP with Prussian blue (ferric ferrocyanide), known for its decorporating efficacy on caesium by oral route, was not done.**

2nd article (1992) - The use of pectin-containing enterosorbents in exposure to radionuclides and heavy metals.
Trakhtenberg IM, Litenko VA, Derevyago IB, Demchenko PI, Mikhailovskii SV.
Lik Sprava 5:29-33 (1992). [Article in Russian]. [Reference 49]

Summary

In1992, Trakhtenberg et al., of the Occupational Illnesses Research Institute in Ukraine, conducted studies on the compound **PVP** developed previously. In a study carried out on animals (female albino rats without offspring) and according to a experimental protocol similar to the studies of Romanenko et al. in 1991 [41], but this time on a total of 96 animals, the efficacy in terms of blockage of the intestinal absorption of ^{85}Sr and ^{137}Cs in foodstuffs by PVP was compared to that of pure citrus pectin and sodium alginate. The novel aspect of this study resides in the fact that PVP was also used while integrated into everyday foodstuffs (bread and sausage). In addition, another compound known as **Karboflavit** and resulting from the combination of **pectin powder, vitamins and activated carbon** was also evaluated. The authors have put forward the hypothesis that the association of pectin and vitamins could enable ^{137}Cs and ^{85}Sr to be linked selectively, whereas the activated carbon could lead to a general detoxification through adsorption of biomolecules of various molecular weights formed in the gastrointestinal tract under the influence of ionising radiation.

As previously, after 30 days of treatment, PVP makes it possible to reduce by 52 % the accumulation of ^{85}Sr and 27 % that of ^{137}Cs in animals ($p<0.05$), the efficacy reaching a plateau from the 14th day in the case of ^{137}Cs. The results show that **PVP could be around twice as effective as pure citrus fruit pectin on the absorption of ^{85}Sr and of equivalent efficacy to that of sodium alginate.**

With regard to **^{137}Cs, the efficacy of PVP could be around 1.5 times higher than that of the two other substances** (pure citrus pectin and sodium alginate) according to the authors. On the other hand, the addition of PVP to bread or sausages appears to slightly reduce the efficacy of the pure PVP. Finally, the **Karboflavit** combination enables a reduction in the accumulation of **^{85}Sr (-40 %)** and **^{137}Cs (-30 %)** compared to animals in the control group, with however **lesser efficacy than that of pure PVP.** Nevertheless, the authors conclude that for a mass prophylaxis, the addition of a preparation such as **PVP to everyday foodstuffs, PVP in the form of tablets** or even combinations such as **Karboflavit**, which combine pectin and activated carbon could enable an efficacious absorption of heavy metals and radionuclides at the intestinal level.

Analysis

In the same way as for reference [41], **no quantities in absolute values for the different compounds** (activated carbon, pectin, supplemented foodstuffs, Karboflavit) are clearly explained. We can only assume that the doses were equivalent in order to be able to validate in a pertinent manner the results of the comparisons. **Other experimental details such as the number of animals per group or the statistical test used for the analysis are also not given.** Moreover, **the mode of contamination of the foodstuffs administered has not been detailed**, the authors being content to state that they are placed under conditions that make it possible to simulate approximately the mode of entry of radionuclides in the body.

In conclusion, this article reports on the feasibility of formulations of foodstuffs supplemented with enterosorbent agents and an association of several "active ingredients" (activated carbon + pectin with added vitamins) **without really having been able to quantify the relative efficacy of any one substance compared to another. Nevertheless, the effect of an intestinal absorbent agent,** whatever it is, on the reduction of the body burden in radionuclides, **remains evident compared to the untreated animals. Nevertheless, this study does not give any sufficiently objective details that allow one to clearly come to a decision on the role of pectin compared to the other substances administered.**

3rd article (2003) – Chronic Cs-137 incorporation in children's organs.
Bandazhevsky YI.
Swiss Med Wkly 133:488-490 (2003). [Reference 5]

Summary

Youri Bandazhevsky published for the first time in an international review his observations on the **chronic incorporation of ^{137}Cs in the bodies of children** living in rural zones of Belarus affected by the fallout from Chernobyl.

These studies concerned children born after March 1987 who were not exposed to radioactive iodine at the time of the accident, even *in utero*. According to the author, the children are contaminated by their mothers' milk and then by consuming cow's milk produced by local farms and by berries, mushrooms or game from the forest. The results of the spectrometric measurements of organs taken in 1997 after **autopsy** concerned **infants** (< 6 months), **children** (52 children less than 10 years old from the Gomel region and studied since 1997) and **adults**.

The results presented in this article show that **^{137}Cs** accumulates more in children than in adults and concentrates in particular in endocrine glands such as the **thyroid** (up to 2054 ± 288 Bq/kg), the **adrenals** (1576 ± 290 Bq/kg), the **pancreas** (1359 ± 350 Bq/kg), the **thymus** (930 ± 278 Bq/kg) and the **skeletal muscles** (902 ± 234Bq/kg), the **spleen** (608 ± 109 Bq/kg) or even the **heart** (478 ± 106 Bq/kg). In the liver, 137Cs concentrates 6 times less (347 ± 61 Bq/kg) than in the thyroid, which remains the organ the most affected. The author underlines the importance of continuing the clinical, epidemiologic, anatomopathologic or experimental studies in order to verify the correlation between this chronic accumulation of the radionuclide in the body with the incidence of pathologies and functional disorders observed in children living in these regions. In terms of curative measurement, it is suggested that the children are placed at least for one month a year in a "clean" environment (sanatorium) where they can be given non contaminated food.

Analysis

This article does not enable a conclusion to be drawn as to a difference in the accumulation behaviour of caesium 137 between children and adults. In fact, the comparative study between the two population groups does not specify at any moment the number of adults studied, the number of children examined only being 6. **Moreover, this study has not been validated by any statistical test that would enable a judgement to be made as to the significance of the differences observed** with regard to the 8 organs sampled in adults and children (myocardium, brain, liver, thyroid, kidneys, spleen, skeletal muscle and small intestine). Finally, the methodology used for measuring the concentration of caesium 137 in the removed organs is not specified and the measurement uncertainties are also not mentioned.

4th article (2003) - Cardiomyopathies au Césium-137.
Bandazhevsky YI, Bandazhevskaya G.
Cardinale XV 8:40-43 (2003). [Reference 4]

Summary

In this article from the journal of cardiology *Cardinale* in French, the work of Youri Bandajevsky and Galina Bandajevskaya describing new forms of ^{137}Cs cardiomyopathias have been reported by Prof. Michel Fernex of the Bale Medical Faculty (Switzerland) and translated from Russian by Wladimir Tchertkoff in 2003.

Work relating to the cardiovascular pathologies observed

In regions in the south of Belarus, anthropogammametric measurements of the population and the spectrometric measurements of organs after autopsy have shown that **children accumulate** in the body **3 to 5 times more ^{137}Cs than adults**, in particular in the adrenal glands, the kidneys, the thyroid gland, the pancreas, the thymus, the skeletal and cardiac muscles, the gut wall and the spleen. Moreover, on **clinical examination**, the **children** showed a high incidence (one child out of two in heavily contaminated regions) of **arterial hypertension, tachycardia** and suffer from **fatigue**, **exertional dyspnoea**, **precordial pain** and sometimes **heart failure**, which may lead to sudden death. **The electrocardiograms (ECG)** of these tired children may show **conduction disorders**, an **incomplete bundle-branch block**, **repolarisation anomalies** and a **pronounced sinusal arythmia**.

Moreover, according to the authors, these **clinical signs** and these **electrocardiographic abnormalities** seem to be **directly proportional to the burden of ^{137}Cs** in the body:

- 0-10 Bq/kg body weight: 80 % of children have a normal ECG.
- 11-36 Bq/kg body weight: 2 children out of 3 have ECG anomalies.
- 37-100 Bq/kg body weight: 80 to 90 % of the children have more pronounced ECG abnormalities.

In **adults**, **cardiac adaptation to effort disorders** occurs for a chronic body burden of caesium greater than 20-30 Bq/kg body weight.

Signs of chronic cardiac insufficiency occur for an average myocardium burden of 136 ± 33 Bq/kg and the anatomo-pathologic examination reveals a **degeneration and a necrosis of the fibres** (myocytolysis with pycnosis of the nucleus) due to the chronic accumulation of caesium. Other organs such as the endocrine glands and the kidneys also show **degenerative attack**: the **thyroid disorder** may contribute to the **cardiac signs** and the **renal attack** could account for the frequency of **arterial hypertension** in this population.

Work relating to the efficacy of pectin

The authors report that an absorbent treatment based on **apple pectin** powder enabled the **^{137}Cs body burden to be reduced** three time more quickly than a diet free of ^{137}Cs and observed a **reversibility of certain symptoms** (study involving 94 children aged from 7 to 17) as well as a **normalisation of the ECG**, providing that the reduction in the ^{137}Cs body burden is significant. On the other hand, **the treatment did not enable the arterial hypertension** of the children to be normalised. The authors conclude on the interest of taking pectin cures for 3 to 4 weeks and repeating them three times a year.

Analysis

Work relating to the cardiovascular pathologies observed

The accumulation of the element Cs and its involvement in the cardiovascular pathologies observed are only based on purely descriptive information provided by the authors. In particular, **no ECG records are given in this article that would make it possible to check the reality of the conduction disorders described.** This point is moreover underlined by the editors of the review, who state in a boxed section introducing the article that *"doubtless we would have liked to have at*

our disposal the analysis of all of the recorded ECGs and the echocardiogram results", adding that *"the dossier includes the essential points, namely the histological examinations of the myocardium and the measurement of the quantity of the isotope in question, caesium 137"*.

Although the study involves anthroporadiametric measurements, no information is given as to the type of equipment used and the conditions for carrying out the examination, and the authors simply state that "the child must remain seated for 3 minutes in the chair". In particular, no mention is made of the counting geometry, the distance between the detector and the child, the importance of the background noise and how it has been taken into account in the results of the measurements taken. Moreover, **the relation between the levels of contamination by caesium 137 and the percentage of ECGs considered abnormal by the authors is not based on any quantitative data**: the conditions under which these results were obtained are not given at any moment, nor the number of children examined, any complementary examinations that may have been carried out to support the diagnosis, etc.

With regard to histological examinations of the myocardium, a single image is given in the document: it concerns "*a 67 year old woman who has lived in a village heavily contaminated by caesium 137*", without any other details being given (level of contamination, name of the village, length of exposure, complementary examinations carried out, conditions of death, etc.). Moreover, the authors do not indicate to what extent the histological anomalies could simply be placed in relation to the living conditions of this patient and the other underlying pathologies that she could have. In this respect, the authors mention a degenerative attack of the endocrine glands and the kidneys, without providing any further details and without any exhaustive description of the histological typology of these pathologies.

Work relating to the efficacy of pectin

With regard to the efficacy of pectin on contamination by caesium 137 and, secondarily, on the cardiovascular disorders observed, although the authors state that the study concerned 94 children aged from 7 to 17, they only describe in detail the case of a young girl aged 14 years in whom was observed the disappearance of an incomplete right bundle-branch block after 16 days of treatment. This conduction disorder was not supported by an ECG record and the other aetiologies of this pathology were not looked for.

To conclude, this article does not in any way enable one to affirm in a scientifically indisputable manner the existence of any relation between the contamination by caesium 137 and cardiovascular disorders observed in children living in the contaminated regions.

5th article (2004) - Reducing the 137Cs-load in the organism of 'Chernobyl' children with apple-pectin.
Nesterenko VB, Nesterenko AV, Babenko VI, Yerkovich TV, Babenko IV.
Swiss Med Wkly 134:24-27 (2004). [Reference 36]

Summary

In this international publication dating from 2004, Nesterenko et al., researchers at the **Belrad** Institute in Belarus, present the results of a clinical study, the objective of which was to evaluate the efficacy of **apple pectin** on the reduction in the ^{137}Cs body burden in children contaminated by Chernobyl and fed a radiologically clean diet.

The randomised clinical trial was carried out on **64 children**, as a **double blind trial compared to a placebo** and after approval by an **ethics committee**. During a stay of one month in a sanatorium, the children were all given a radiologically "clean" diet and were divided into 2 groups: 32 children were given a supplement of **5 grammes of powdered apple pectin** (containing **15 to 16 % of pure pectin**) diluted in water, **twice a day** at mealtimes for **3 weeks**; the 32 other children were given a placebo powder under the same conditions.

Anthropogammametric measurements were carried out at the start and the end of the clinical trial and showed that before the cure, the children all had an average caesium 137 body burden of **30 Bq/kg** body weight. **At the end of the cure, a reduction in the ^{137}Cs body burden was observed in all of the children; however, those who were given pectin had a reduction of more**

than 62.6 % of the ^{137}Cs body burden (final burden of ^{137}Cs around 11.3 Bq/kg), in other words an efficacy 4.5 times superior to the control group, in which the reduction was only 13.9 % (final burden of ^{137}Cs of 25.8 Bq/kg). This difference between the two groups was considered as significant ($p<0.01$). No problem of intolerance to the treatment was observed. The authors conclude that this type of treatment protocol with apple pectin enabled a significant reduction in the radionuclide body burden in less than 3 weeks at the rate of an accumulation less than 20 Bq/kg, the threshold value that Bandazhevsky considers as potentially associated with the onset of specific tissular pathologies.

Analysis

The protocol of this clinical trial appears, overall, to be both correct and well documented. The withdrawal of 6 children before the end of the trial is clearly explained and the final number of children taken into account in each group is satisfactory in statistical terms (n = 28 in the control groups, 14 girls/14 boys; n = 30 in the treated group, 15 girls/15 boys), even though no details are given of the type of statistical test used.

A natural reduction in the level of caesium incorporated in the body (-14 %), in all likelihood following the stoppage of the ingestion of contaminated food, emerges from this study. It would appear that the daily administration of pectin to these children over a period of 3 weeks leads to a more important reduction in the quantity of caesium measured in the body, of around 63 %, which suggests a beneficial effect of pectin on the decorporation of caesium from the body. **However, it should be pointed out that the authors do not give details at any stage of the uncertainties associated with the measurements carried out, which means it is not possible to verify for each child included in the study whether there effectively exists a significant difference between the measurements carried out before and after the administration of the treatment (pectin or placebo).**

Furthermore, this study does not enable any decision to be made with regard to the efficacy of pectin in those children who continue to consume local products. In order to obtain such data, it would be necessary to put in place an equivalent protocol involving children living in their normal context and who consume contaminated food.

6th article (2004) - Relationship between caesium (137Cs) load, cardiovascular symptoms, and source of food in 'Chernobyl' children – preliminary observations after intake of oral apple pectin.
Bandazhevskaya GS, Nesterenko VB, Yerkovich TV, Bandazhevsky YI.
Swiss Med Wkly 134:725-729 (2004). [Reference 3]

Summary

In this article dating from 2004, Bandazhevskaya et al. report the results of a study carried out 17 years after the Chernobyl catastrophe. This study concerns the relations between the ^{137}Cs body burden in contaminated children, their food source and the cardiovascular symptoms observed. The preliminary results of the effect of an oral treatment with apple pectin on these symptoms are also set forth. The clinical study concerned 94 children aged from 7 to 17 years old and divided into three groups as a function of the initial level of contamination determined by spectrometry:

- Group 1: n = 33 (16 girls/17 boys, average age 10.8 years/12.5 years) with low contamination levels (less than 5 Bq/kg)
- Group 2: n = 31 (17 girls/ 14 boys, average age 12.8 years/12.2 years) with moderate contamination levels (38 ± 2.4 Bq/kg)
- Group 3: n = 30 (12 girls/18 boys, average age 12.7 years/12.7 years) with high contamination levels (122 ± 18.5 Bq/kg)

The consumption by the children of foodstuffs produced in local farms (milk, vegetables grown on contaminated ground or fertilised with ash from contaminated forests) or the forest itself (wild mushrooms and berries) concerns 19 children (58 %) of group 1, 22 children (71 %) of group 2 and 30 children (100 %) of group 3. Furthermore, **a correlation and a proportionality** between the **level of**

contamination and the incidence **of cardiovascular symptoms in the children, such as abnormal heart sounds** by auscultation, **arterial hypertension** or **hypotension**, or even an **abnormal ECG** (significant difference between the 3 groups ($p<0.05$)) was established.

The children in groups 2 and 3 were given an oral treatment of **Vitapect® pectin**, according to the following protocol: 5 grammes of pectin powder (containing 16 % of pure pectin) diluted in water, twice a day during meals and for a total length of 16 days. This treatment enables a **significant reduction** ($p<0.05$) of body burdens of **39 %** (from 38 to 23 Bq/kg) and **28 %** (from 122 to 88 Bq/kg), respectively in the moderately contaminated group (group 2) and heavily contaminated group (group 3).

This body burden reduction was accompanied by a **significant improvement in the number of pathological ECGs** (at the end of the study, the count went from 72 % to 87 % of normal ECGs in group 2, and from 79 % to 93 % of normal ECGs in group 3) ($p<0.05$). On the other hand, the **cardiovascular symptoms** and the **arterial hypertension were not improved** in a significant manner by the pectin treatment.

The length of treatment of 16 days was considered too brief to further reduce the ^{137}Cs body burden, particularly in children with a heavy initial contamination. In order to determine if the treatment with pectin could improve the clinical signs, the authors suggest that other double blind, placebo comparison clinical trials should be planned on a larger population of children with different levels of contamination.

Analysis

This study aims to assess the health consequences, particularly in terms of the incidence of cardio-vascular symptoms, of an administration of pectin over a period of 2 weeks. ECG record abnormalities are observed in most of the children, but **no information is provided as to the precise nature of the abnormalities** (conduction disorders, auricular rhythm disorders, ventricular rhythm disorders, etc.), **the authors make do with speaking of pathological ECGs and abnormal heart sounds, without these being precisely characterised.**

An improvement in the ECG appears to be induced by pectin in the groups of children contaminated by caesium, with a reduction in the incidence of around 15 %. It should however be pointed out that **50 % of the non contaminated children also have an impaired ECG, a particularly high incidence. Consequently, this data absolutely does not enable one to come to a conclusion as to a possible cause and effect link between contamination by caesium 137 and cardiovascular rhythm disorders.**

Moreover, no mention is made at any stage of searching for other aetiologies of these disorders. **It is therefore indispensable, even before setting up a clinical study aimed at evaluating the efficacy of pectin in these children, as has been proposed by the authors, to very precisely characterise the nature of the cardiovascular disorders and to study all of their possible causes, particularly by carrying out cardiac ultrasounds.**

In addition, the authors state in their article that the more contaminated the children by caesium 137, the more they suffer from thoracic pain, headaches, irritability, bleeding noses, fatigue and depressive syndrome. However, **the authors** do not make clear what clinical examinations enabled the presence of such pathologies to be affirmed and, above all, **do not state whether such disorders evolved during the course of the treatment and do not look for their other possible aetiologies, such as a nutritional deficit, unhealthy living conditions, etc.**

Furthermore, it should be pointed out that an admittedly minor error exists in the sex ratio indicated by the authors, who state that the study was conducted on 94 children, made up of 46 boys and 48 girls. However, the summation of the boys and girls from each of the 3 groups gives a total of 45 boys (16 + 17 + 12) and 49 girls (17 + 14 + 18).

Finally, with regard to the efficacy of pectin on the reduction of contamination by caesium 137, **the authors do not provide any explanation as to an apparently higher efficacy in moderately contaminated children (- 39 %) than in heavily contaminated children (- 28 %).**

2.2 Analysis of documents not published in scientific reviews and that give the results of experimental work

1st document (2003) - Method recommendations for the use of Zosterin-Ultra pectin as an agent of mass prevention at enterprises of the nuclear and other sectors of industry working with radioactive substrates, heavy and polyvalent metals, as well as in areas contaminated by radioactive and other hazardous substances.
Russian Federation Ministry of Public Health. February 10 (2003). [Article in Russian]. [Reference 44]

Summary

In this 2003 report, the Russian Ministry of Health sets out its recommendations for the use and the directions for use of a product based on zosterine, the pectin from an aquatic plant (Zostera) known as **Zosterin-Ultra®,** as a mass prophylaxis agent in the nuclear industry or in companies using radionuclides, heavy metals and polyvalent metals, and in zones contaminated by radioactive or toxic substances.

Zosterine contains fractions of low molecular weight **capable of entering the bloodstream** and exhibiting **sorption properties in the body**. The presence of **apiose** sugar residues in the zosterine molecule enhances the sorption capacity of this agent and prevents the enzymatic degradation of pectin at the level of the colon. As non-assimilated pectin, the injection of zosterine into the bloodstream does not lead to a rupture in nutrition, metabolism or other functions. In 1993, the Russian Ministry of Health already recognised the **immunomodulatory**, antiviral, antibacterial, radiation protection and **antihaemorragic properties** of zosterine and its use as a treatment or a prophylactic agent in the **lead**, **zinc** or **other polyvalent metal** industries. The commercial product **Zosterin-Ultra®,** used in liquid form and intended to be administered by oral route, was approved by the Ukrainian Ministry of Health in 1998, and later by the Russian Ministry of Health in 1999, **as a biologically active (or therapeutic) food additive** endowed with **enterosorption and hemosorption properties.**

The research and the clinical trials carried out in institutes of medicine (MRRC Obninsk) and biophysics (IBPh Moscow) in Russia has demonstrated that this agent is capable of eliminating from the body toxic compounds such as **lead**, **mercury** (acceleration of excretion by a factor of 2.74 in 94.5 % of children), **cadmium**, **zinc**, **manganese** and **nickel** (acceleration of the urinary excretion of Mn and Ni by more than a factor of 2 over the first few days and practically a factor of 3 after 15 days) as well as other heavy metals or radionuclides such as **plutonium** (increase in the urinary excretion by a factor of between 1.41 and 2.74). Moreover, Zosterin-Ultra® could also be efficacious in the symptomatic treatment of other pathologies such as ulcers, hepatitis, intestinal dysbacteriosis or even allergies of various origins. The recommended dosage in the prevention of intoxications by radionuclides or heavy metals is 0.5 grammes (1 sachet) to be dissolved in 100 ml of hot water and to be drunk within 2 hours of the last meal, for a period of 10 to 12 days. This protocol may be repeated after an interruption of 10-12 days. In a contamination treatment cure, the doctor may prescribe 0.5 to 1 gramme of zosterine over a period of 10 to 20 days in adults and 0.25 grammes to be dissolved in 50 ml hot water each day for 10 to 15 days in children aged from 3 to 12 years.

Analysis

Zosterine (oligogalacturonate), which is a natural extract from a seaweed (Zostera), appears to be very interesting for treatment or mass prophylaxis by oral route, which could not be envisaged with other antidotes (such as Prussian Blue or DTPA for example) in the event of exposure or contamination by various heavy metals or even radionuclides such as actinides (plutonium). However, and since zosterine has been presented as potentially capable of being resorbed in the intestine and acting within the body, the molecule should then be considered as a medicating active ingredient or antidote and no longer as a simple food supplement as is the case with other pectins that, for their part, only act in the gastrointestinal tract.

Consequently, **it would be desirable to complete the dossier by data or by a more complete study of the pharmacokinetics** (absorption, distribution, metabolism, and excretion), the pharmacology (mode of action in the blood stream and on the organs and dose effect) **or even the**

longer term toxicology of zosterine, information that is not given and is missing from this report. Failing this, the only indirect proof of a systemic action of zosterine resides in the acceleration of the urinary elimination of certain metals or toxic substances, probably in forms that complex with zosterine.

2nd document (2004) - Final report on work of the third phase in the project Highly-Irradiated Children in Belarus (fourth stage) – Effective removal of ^{137}Cs radionuclides from children by the Vitapect pectin-containing product and preservation and stabilization by it of the balance of vital trace elements (K, Zn, Fe, Cu).
Belrad Institute of Radiation Safety. Minsk, Belarus, April 11 (2004). [Article in Russian]. [Reference 8]

Summary

This document, written in 2004, constitutes the final report of the third phase in the project "Highly-Irradiated Children in Belarus" of the Belrad Institute. The results of a clinical study of the efficacy of Vitapect® on the elimination of ^{137}Cs in children and the effects of the treatment on the balance of trace elements (K, Zn, Fe, Cu) in the body are detailed. The studies were conducted between November 2003 and April 2004 in two clinics in the region of Gomel in Belarus in collaboration with the Juelich Research Institute in Germany. The study as a whole concerned a total number of **406 children**, among which 2 groups of **50 children** participated in a **double blind clinical trial** to test the efficacy of **Vitapect®** compared to a **placebo** under the control of an **ethics committee**. This treatment consisted in the administration of **5 grammes of Vitapect® or placebo twice a day for 12 to 14 days.** Measurements of specific activity of ^{137}Cs were carried out on each child before the start of the treatment and 8 measurements were carried out during the trial in order to monitor the evolution of the radionuclide body burden. The radioactive content of the food was also checked. Measurements of the quantity of trace elements (K, Zn, Cu, Fe) were conducted in 67 to 99 treated children (as a function of the element assayed) and in 29 to 34 children (as a function of the element assayed) of the placebo group.

The results of the treatment by absorbent agent indicated that **Vitapect®** makes it possible to reduce significantly more of the body burden in ^{137}Cs over a period of 12 to 14 days (efficacy in terms of reduction in the burden of between **22 % to 41 %**, $p<0.01$) than the **placebo** (efficacy between **12 % and 21 %**, $p<0.01$) or even after consuming **radiologically "clean" food only** (**24 %** reduction on average, $p<0.01$). No treatment however enabled **a significant improvement in ECG disorders.** The authors suggest that the observation period of 14 days is probably too brief to see the benefits of the treatment on the ECG records. The functional test revealed that the treatments did not enable hypertonic or hypotonic type vascular reactions after moderate physical exercise to be corrected in a significant manner. On the other hand, **a significant increase** in the percentage of **vascular reactions following physical effort** was observed following treatment with **Vitapect®** ($p<0.01$). As regards the electrolytic balance, the pectin treatment did not induce any major imbalance in the plasmatic concentrations of trace elements: only a **slight drop in Zn** ($p<0.01$) and a **slight increase in plasmatic Cu and Fe** ($p<0.01$) were observed, without any concentrations falling outside of the **limits of normal values**.

The authors conclude from this clinical study that Vitapect® makes it possible to efficaciously reduce the ^{137}Cs body burden in children after 12 to 14 days of treatment while at the same time preserving the trace elements K, Zn, Cu and Fe in the body. Moreover, the authors suggest that the study should be repeated over a longer time period of 21 days of treatment with pectin, in keeping with the normal procedure of a cure of 3 weeks in a sanatorium.

Analysis

Although at first glance the number of children examined appears to be satisfactory in statistical terms, **the description of the methodology employed by the authors in this study is, to say the least, confused and imprecise.**

With regard to the efficacy of pectin on the concentration of caesium 137, the study concerned 50 children who were given pectin and 50 children who were given a placebo, and the respective

numbers of children were well balanced in this respect. On the other hand, as regards the children placed in the second sanatorium in which they were given "radiologically clean" food, the total number of children was 244 subjects, the results obtained could not therefore be laid beside the previous ones given the much larger sampling. Moreover, it is surprising to note that, **although the authors provide information relating to the reduction in the concentration of caesium for the children treated (by pectin or placebo) for each visit, the same is not true for the group of 244 children. Furthermore, the authors limit themselves to giving the reductions in the concentration of caesium expressed as percentages and only give averaged quantitative data.** Moreover, this document discloses an increase in the specific activity of ^{137}Cs in children between the 3rd and the 5th measurement and between the 6th and the 7th measurement, despite radiologically "clean" food. This trend, highlighted in the two groups observed (group Vitapect® and group placebo), is not commented on by the authors.

Finally, the authors do not provide formal proof that this study has been carried out under proper double blind conditions: indeed, after having stated that the anthroporadiametric measurement results are transmitted to the assistant medical officer, it is stated that the head of the medical department chooses to divide up the children selected in the pectin group or in the placebo group as a function of the available results, which runs contrary to any procedure supposed to be carried out under double blind conditions.

With regard to the studies termed medical studies, the relative numbers of subjects in the group of children treated with pectin and the group of children given the placebo are manifestly unbalanced in favour of the pectin group. Moreover, the numbers in each group differ as a function of the examination carried out without the authors providing any explanation. **Moreover, inconsistencies and even contradictions in the results presented strongly call into question the seriousness of this study.** For example:

- **With regard to the ECGs: 106 "pectin" children and 36 "placebo" children are concerned.** It should be noted that in the table giving the breakdown of ECGs as a function of the observed disorder, we then have **112 "pectin" children** (instead of 106) and **35 "placebo" children** (instead of 36). Then, a figure showing the breakdown between the normal and pathological ECGs as a function of the bodily concentrations of caesium 137 discloses further on in the document that **543 ECGs were carried out**, whereas a little before that in the document, the authors state that **406 ECGs were carried out**, 301 of which were considered as pathological and 105 as normal. Furthermore, returning to the first paragraphs of the article, we in fact learn that **147 children benefited from an ECG when they arrived at and departed from the sanatorium**, and that **259 children benefited from an ECG only when they arrived** (thus signifying that the effects on the ECG of any treatment or radiologically clean diet can reasonably be characterised on at least 259 children).
- **With regard to the arterial pressure measurements**: 88 "pectin" children and 26 "placebo" children are concerned. **No quantitative result of the measured arterial tension values is provided by the authors,** who are content to speak of "normotonic", "hypotonic" or "hypertonic" reactions without the reader having the slightest idea of the precise signification of these observations.
- **With regard to the measurement of the quantity of potassium**: 99 "pectin" children and 31 "placebo" children are concerned.
- **With regard to the measurement of the quantity of zinc**: 93 "pectin" children and 34 "placebo" children are concerned.
- **With regard to the measurement of the quantity of copper**: 67 "pectin" children and 30 "placebo" children are concerned.
- **With regard to the measurement of the quantity of iron**: 87 "pectin" children and 29 "placebo" children are concerned.

With regard to the measurements of the quantities of minerals (K, Zn, Cu, Fe), only the breakdown of results of the assay measurements carried out on "pectin" children are given in the document, depending on whether they are normal, worse than or better than normal. Whereas in

the description of the methodology used, the authors mention the assay measurements carried out on "placebo" children (as indicated above), we learn at the end of the article that in fact **no result is available for the "placebo" group** due to financial difficulties and the refusal by the children and the parents to have blood samples taken. **Not only is there an obvious contradiction in what the authors say, but in addition, it is incomprehensible for the blood sampling to be accepted by the children of the "pectin" group and systematically refused by the children of the "placebo" group.**

Moreover, the results relating to the effects of treatments on certain cardiovascular symptoms of this 2003 study do not agree with those of the previous study carried out in 2001 and published in 2004 (reference [3]). Contrary to this latter study conducted over a period of 16 days, involving the same product Vitapect® and concerning a total of 61 children, **the treatment by pectin does not improve the pathological ECGs observed in the children.** As regards the electrolytic balance, the results presented by the authors cannot be taken into consideration in the sense that we learn in another referenced document [37] that the product Vitapect® is in fact supplemented with potassium (K^+), zinc (Zn^{2+}), selenium (Se^{2+}) and calcium (Ca^{2+}). **Therefore, it is not objective to affirm that the treatment by pectin does not significantly affect the plasmatic concentrations of trace elements in the body. To back up this affirmation, it would be necessary to conduct the same type of study by administering pectin alone in order to verify whether this food additive cannot effectively be the source of mineral deficiencies.**

Finally, given the numerous inaccuracies, inconsistencies and contradictions noted in this article, no objective conclusions may be drawn from this study.

2.3 Analysis of reports not published in scientific reviews and that do not give the results of experimental work

1st report (2000) - Ecological de-adaptation syndrome in children of Belarus and ways to correct it – Method recommendations.
Belarus Republic Ministry of Public Health. Minsk, Belarus, June 9 (2000). [Article in Russian]. [Reference 6]

Summary

This report, drafted in 2000 by the Belarus Ministry of Health, describes the "Ecological de-adaptation syndrome in children of Belarus and ways to correct it". This term is taken to mean the development of symptoms due to the combined effect of a series of xenobiotics (substances foreign to the body such as radionuclides for example) when the concentrations of each taken separately are too low to induce specific modifications in the body (symptoms or specific syndromes). In this syndrome, xenobiotics or radionuclides give rise to transmitters or receptors in cellular interaction systems, thus reducing the tolerance threshold, resistance or even the functional adaptation reactions of the neuroendocrinian or immune systems.

A series of methods are proposed to correct this syndrome: it is pointed out that only preventive measures employing the least possible amount of exogenous medicines or drugs (molecules themselves considered as ecopathogenic factors) but favouring different non-invasive agents and methods that make it possible to increase in a general manner the resistance of the body when faced with aggressive factors from the environment should be considered.

These methods consist in eating a "sensible" diet, in other words composed of ecologically pure products (amino acids, polyunsaturated fatty acids, vitamins, trace elements, phytotherapeutic products, etc.), to do physical exercises (in order to activate the cardiovascular system, improve urinary excretion, stimulate the secretory and digestive functions, stimulate the perspiration processes and enhance the exhalation of toxic substances), favour the elimination of xenobiotics through the ingestion of food additives (pectins, carbon) and to carry out lymphatic drainages.

Analysis

This document does not provide any additional information as to the efficacy of pectin on the elimination of xenobiotics from the body. It only details the posologies for several specialities containing pectin, such as:

- MEDETOPECT® (France): 3 to 4 tablets a day for 7 days then 4 to 10 a day for the next 7 days.
- VITAPECT® (Ukraine): 1 to 2 coffee spoons 2 to 2 times a day.
- Pectin tablets from the Plonta KOGKP pharmaceuticals company (Ukraine, authorized in Belarus since May 1994): 3 to 5 grammes a day for 10 to 14 days.

2nd report (2002) - Final report of the international expert analysis of the Belrad Institute of Radiation Safety – Radiation monitoring on HRS of children in Belarus Chernobyl region, their effective radiation protection by pectin products and the urgency of issuing the pectin-based food additive Vitapect in the Republic.
Belrad Institute of Radiation Safety. Minsk, Belarus, July 20 (2002). [Article in Russian]. [Reference 7]

Summary

This document presents an analysis of the activities and the projects of the **Belrad** Independent Radiological Protection Institute (Belarus) by an international committee of experts. The efficacy of a radiological surveillance of children from the Chernobyl region in Belarus thanks to **human radiation spectrometers (HRS)** and the efficacy of radiation protection products based on **pectin**

have been evaluated. The experts were also invited to rule on the interest and urgency of a commercialisation in Belarus of **Vitapect®**, the pectin based food additive.

The experts approved the emergency measures proposed by the Belrad Institute and recognised the necessity of a **radiological surveillance of the diet** of families living in the region of Chernobyl (M. Fernex), and the importance of **radiological measurements on children** by means of **HRS** devices in order **to determine the level of accumulation of ^{137}Cs in their bodies** (Ye.A. Yakovlev). In their opinion, a preventive treatment by the **pectin** food additive conducted 3 to 4 times a year could be a suitable method **for reducing the annual dose by a factor of 2 to 3**: a consumption up to 15 grammes of pectin with food would be desirable to eliminate radionuclides and heavy metals from the body (N.D. Kolomiyets).

The experts commented on the interest of the theoretical work conducted by the Institute with the aim of demonstrating, firstly, the link between the degradation in the state of health and the presence of radionuclides in children and, secondly, the improvement in their health after elimination of the radionuclides (Ye.B. Burlakova). An operational schema is proposed to significantly reduce the radiological burden in children in contaminated regions of Belarus: the examination by HRS and the prescription and the dispensation of a food supplement based on pectin (A.V. Yablokov).

Finally, the experts make it clear that HRS measurements do not constitute an actual medical examination (M. Fernex, N.D. Komoiyets) and that the production and the commercialisation of a pectin based food supplement such as Vitapect® in Belarus would constitute an economically justified emergency measure to care for the children (M. Fernex).

Analysis

This document is presented as a critical analysis, by a committee of international experts, of work carried out by the Belrad Institute on the surveillance of children living in contaminated areas of Belarus and on the interest of administering pectin to them in order to cut their level of contamination by caesium 137. **This report does not reasonably enable an objective judgment to be made on the pertinence of the work analysed** in the sense that it only ratifies the results obtained without any real analysis being presented.

3rd report (2005) - Consequences of the Chernobyl accident for Belarus and urgency of radiation protection of the population, especially children.
Nesterenko VB.
Report at the international symposium « *Prevention of the risks. Let's learn the lessons of Chernobyl* ». Lyon, France, April 1-2 (2005). [Reference 37]

Summary

In this symposium report on the consequences of Chernobyl, which was held in April 2005, Vassili Nesterenko states that more than 2.5 million people, including more than 500 000 children, are concerned by chronic exposure to radioactivity. This internal contamination could be due to long lifetime emitters such as ^{137}Cs and linked to the consumption of food contaminated and produced locally in the affected regions.

Since 1996, at the initiative of the Belrad Institute (Belarus) and thanks to international funding (Ireland, Germany, United States, Norway), spectrometric measurement campaigns of the population by mobile laboratories were able to be conducted and the levels of contamination by ^{137}Cs that can exceed 15 to 20 Bq/kg (which corresponds to a dose > 0.1mSv/y) have been recorded in more than 70 to 90 % of the children. In certain villages, the levels can attain 6700 to 7300 Bq/kg and more than 33 % of the children are likely to be exposed to a dose exceeding 1mSv/y. Moreover, it has been demonstrated that pathologies of the vital systems transpire above a body burden of 50 to 70 Bq/kg.

In 1996, the Belrad Institute initiated the distribution of pectin based enterosorbent treatments (Medetopect®, France; Yablopect®, Ukraine) to accelerate the excretion of ^{137}Cs in children. Since 2000, the Institute has begun the production of a food additive that has been approved by the

Ministry of Health in Belarus: **Vitapect®** powder, composed of **pectin** and supplemented with **vitamins B_1, B_2, B_6, B_{12}, C, E, beta-carotene, folic acid** and the trace elements **K, Zn, Fe and Ca.** More than 75 000 children have been able to be treated with Vitapect® and several clinical trials conducted between 2001 and 2003 in sanatoriums have made it possible to show that such **pectin based enterosorbent products** would make it possible **to reduce by a factor of 2 to 3 the ^{137}Cs body burden** and thus **to bring about an improvement in the health of the children** (according to the **ECG results**) **without causing any depletion in essential elements (potassium, copper, zinc or iron)** (medical part of the project "Highly exposed children of Belarus" of the Belrad Institute).

Finally, according to V. Nesterenko, the German Federal Radiation Protection Commission stated on the 22 March 2005 in its final report on the evaluation of the studies conducted by Belrad that pectin based preparations could constitute a radiological protection preventive measure for the population and contribute to reducing annual exposure to radiation.

V. Nesterenko concludes by stating that **international aid** would make it possible **to continue the studies** in order to identify the relationships between the doses and the incidence of pathologies (cardiac, renal, ocular, endocrinous, etc.) in children, to increase the number of laboratories and measurement systems and **radiological surveillance of foodstuffs and the population** and, finally, to increase **the production and the use of pectin based enterosorbent agents** in the form of food additives.

Analysis

This document does not give rise to any particular comment in the sense that it only discusses data already analysed in other articles. **However, it should be noted that the approval by the German Federal Radiation Protection Commission as to the fact that pectin based preparations could constitute a radiation protection preventive measure has not been able to be verified in any written document.**

3. Synthesis

3.1 Analysis of the bibliographic search carried out

The scientific basis on which the bibliographic analysis undertaken is based was constituted from a search carried out by means of the principal search engines and data bases used by the international scientific community. The conclusions that may be drawn from this bibliographic search are, firstly, **that very few articles concerning the biological and medical effects of pectin in the event of incorporation of radionuclides have been published in international scientific reviews** and, secondly, that **the reviews disclosing studies on pectin as a decorporating agent of caesium 137 have very low scientific renown.**

Thus, a search undertaken with the "Pub Med" search engine, came up with the following results, depending on the key words used:

- Key word "PECTIN": 2 486 articles referenced.
- Key words "PECTIN" and "METAL": 177 articles referenced.
- Key words "PECTIN" and "RADIONUCLIDE": 31 articles referenced.
- Key words "PECTIN" and "CAESIUM": 5 articles referenced.

Among the 5 references obtained from the key words "pectin" and "caesium", 4 directly concerned the role of pectin in the event of contamination by caesium 137. These are references [3], [36], [41] and [49], which correspond to the articles published in the reviews "Swiss Med Weekly", "Lik Sprava" and "Gig Tr Prof Zabol".

In order to evaluate the scientific renown of these review, we investigated the **impact factor**, IF, which represents, for a given year, the ratio between the number of citations compared to the number of articles published by a journal, extending over a reference period of two years. This indicator therefore measures the average frequency with which all of the articles of the journal in question are cited over a defined period. It therefore gives a rating from the visibility of a review, which makes it possible to assess the interest shown in it by the international scientific community. By way of example, the review "Nature" has an impact factor of 25.4, while the review "Endocrinology" has an impact factor of 4.4.

The impact factors of the 3 reviews cited above are 1.162 for "Swiss Med Weekly" and equal to 0 for "Lik Sprava" and "Gig Tr Prof Zabol". This therefore signifies that, **not only have very few articles been published on the role of pectin as a decorporating agent of caesium 137, but also that they have been published in reviews with extremely low impact factors,** thus indicating the little amount of work carried out on the subject and the absence of scientific renown of the reviews in question. Moreover, it should be pointed out that certain articles concerning the role of pectin vis-à-vis caesium 137 are not referenced by the "Pub Med" search engine; obviously, these articles were analysed within the scope of this report.

In order to complete this analysis of the bibliographic search undertaken, we classified the bibliographic references used in the drafting of this report into 4 categories, according to the subject to which they pertain ("Human nutrition", "Heavy metals", "Radionuclides" and "Caesium") then, for each of these categories, we calculated the average impact factors of the review cited. It should be noted that the documents not published in scientific reviews were not taken into consideration in this analysis and that certain articles could concern several of the chosen categories.

Figures 2 and 3 give the results of this analysis. They confirm that the role of pectin in human nutrition has been the subject of numerous studies, the results of which have been published in scientific reviews with a relatively high impact factor. On the other hand, with regard to the role of pectin in the event of exposure to heavy metals and/or incorporation of radionuclides, including caesium 137, this analysis of the bibliographic search confirms that these subjects have been the subject of very little work in which the international scientific community has shown relatively little interest, the average impact factors for the reviews being below 1 for the 3 subjects.

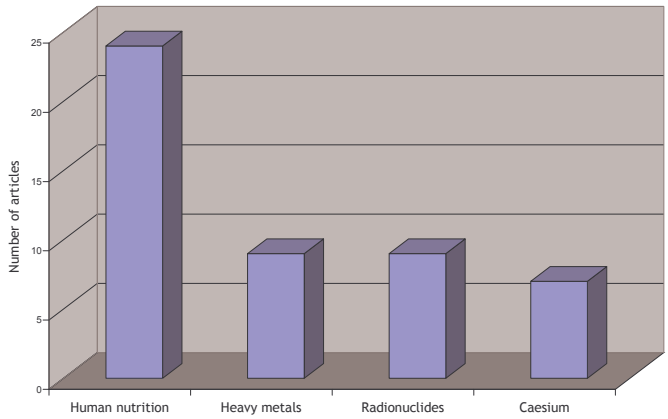

Figure 2: Breakdown of the number of articles in each subject category

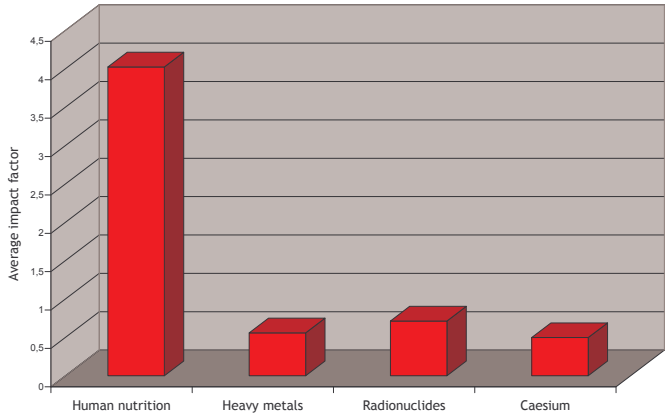

Figure 3: Average impact factor

Nevertheless, this observation does not signify in any way that these subjects are not of scientific interest but simply that the research teams working in the field were not until then aware of them.

3.2 Synthesis of documents on the biological and medical effects of pectin in the event of chronic incorporation of radionuclides

3.2.1 Synthesis of articles published in scientific reviews

The studies described by the authors in these articles were obtained during experimental studies conducted on rats and clinical studies conducted on children living in the contaminated regions. As an initial analysis, the results of these studies show that pectin could make it possible to reduce by around 27 % the levels of contamination in rats and around 28 to 63 % the levels of contamination in children. Moreover, the authors observed cardiovascular disorders in the contaminated children, with caesium 137 being mainly concentrated in the thyroid and the heart.

These articles present results that absolutely have to be checked within the framework of new studies, wherein the methodology cannot be criticized in any manner. Indeed, these documents raise numerous questions that do not allow one, as things stand, to come to a clear decision on the interest of administering pectin with the aim of decorporating caesium present in the body.

For example, the work described does not enable any conclusions to be drawn as to the relative efficacy of pectin compared to other constituents of the administered mixtures, on the efficacy of pectin outside of any ingested foodstuff, on the relation between the levels of contamination by

caesium 137 and the cardiovascular disorders observed, and on the accumulation differences observed between the different organs.

Moreover, the methodology used suffers from numerous imprecisions: for example, although the numbers of children studied appears to be satisfactory, the statistical exploitation of the results makes no mention of the associated uncertainties or of the tests used, which would enable the reader to decide on their significance compared to the control group.

Finally, no comparative study of the efficacy of pectin compared to that of Prussian blue was undertaken, even though Prussian blue has been considered, until now, as the reference treatment for contaminations by caesium 137.

3.2.2 Synthesis of documents not published in scientific reviews and that give the results of experimental work

The only lesson that may be drawn from the documents analysed concerns the potential interest of zosterine, the natural extract of a seaweed, on the decorporation of caesium 137. This work offers interesting study perspectives but which need to be completed by experimentations that will make it possible to evaluate the action mechanism, the evolution in the body and the toxicity of zosterine, before seriously envisaging it being administered to humans.

The second document analysed (reference [8]) does not provide **any objective element that enables a verdict to be pronounced as to the efficacy of pectin as a decorporating agent of caesium 137.** The methodology used by the authors is open to strong criticism and the results presented are not only inconsistent but also contradictory.

3.2.3 Synthesis of reports not published in scientific reviews and that do not give the results of experimental work

These reports, just like the previous reports, do not provide an additional information compared to the published studies. Moreover, since they involve the evaluation of the work of the Belrad Institute by a panel of international experts, they do not enable the reader to objectively draw conclusions as to the real interest of the studies that have been conducted. **To do this, it would be necessary for this work to be analysed by a group of experts representing the whole international scientific community.**

In conclusion, the question of the role of pectin in dealing with contaminations by caesium 137 remains an open question because the documents analysed do not make it possible to either confirm or invalidate its role in such an indication. In fact, the data presented in the international literature is insufficient or of contestable scientific quality.

Thus, an expert appraisal based only on the data available in the literature does not enable one to pronounce judgement on the efficacy of pectin for treating contaminations by caesium 137.

Only experimental studies on animal models and clinical studies, the protocols of which must meet the conventional criteria recognised by the international scientific community, will provide the information indispensable to the evaluation of the role that pectin could play in children living in regions contaminated by fallout from the Chernobyl nuclear plant.

The following chapter presents proposals for studies that should be put in place to answer the question being posed.

4. IRSN proposals

4.1 Clinical research proposals

Clinical studies conducted on children living in regions contaminated by caesium should provide answers to the following questions:

- Question 1: What is the efficacy of pectin as a decorporating agent of caesium introduced *via* contaminated foodstuffs?
- Question 2: What is the relative efficacy of pectin compared to other substances entering in the composition of the administered mixtures?
- Question 3: Can the administration of pectin lead to vitamin and mineral deficiencies?
- Question 4: Does a cause and effect relationship exist between chronic contamination by caesium 137 and the existence of associated cardiovascular disorders?
- Question 5: What is the efficacy of pectin on the evolution of cardiovascular disorders in children living in regions contaminated by caesium?
- Question 6: Do differences of accumulation of caesium 137 exist within organs such as the heart?

In order to answer all of the questions listed above, it will be necessary, firstly, to select the children that should take part in the clinical studies and, secondly, devise appropriate protocols.

4.1.1 Methodology to use for constituting the populations of children to be included in the study protocols

In order to have available the basic data necessary to interpret the results of the clinical studies organised, each child included in the protocols should benefit from the following examinations before any treatment by pectin is put in place:

- Anthroporadiametric measurements of the retention of caesium 137 at the level of the whole body: this examination will make it possible to determine **the breakdown of concentrations of caesium 137 as a function of the age, sex and the weight of the child and the type of diet.**
- Anthroporadiametric measurements of the retention of caesium 137 at the level of the myocardium and at the level of the skeletal muscle (for example, the thigh muscle): this examination will make it possible to determine **if the cardiac muscle has a specific tropism for caesium 137.**
- Taking of an electrocardiogram and cardiac ultrasonic scan: these examinations will enable **any cardiovascular disorders pre-existing within the studied populations to be identified**; the results obtained must then be compared to equivalent populations who do not live in the regions contaminated by caesium 137.
- Search for all aetiologies, other than a contamination by caesium, which could be responsible for cardiovascular disorders: this study will then make it possible to pronounce judgement on **a possible relation between contamination by caesium 137 and cardiovascular disorders.**
- Dosage of the principal vitamins (vitamin A, vitamins of the B group, vitamin C, vitamin D, vitamin E, folic acid) and the principal minerals (potassium, zinc, copper, iron): these examinations will make it possible to have available **data relating to the nutritional state of the children** and will constitute “zero points” before pectin treatments are embarked on.

4.1.2 Evaluation of the efficacy of pectin as a caesium 137 decorporating agent

Two types of clinical studies should be set up, as a function of whether the children included in each study continue or not to consume foodstuffs contaminated by caesium 137. The studies will go on for 3 weeks, as suggested by the authors of the documents analysed within the scope of this report.

The first study will concern three groups of children stemming from the populations described above and who **continue to consume foodstuffs contaminated** by caesium 137 throughout the protocol:

- The first group will receive, on a daily basis, a treatment based on apple pectin, to the exclusion of any other associated substance.
- The second group will be given a placebo on a daily basis.
- The third group will be given, on a daily basis, a treatment based on a speciality containing, among other things, apple pectin (for example, Vitapect®).

The second study will concern three other groups of children stemming from the populations described above but who **do not consume foodstuffs contaminated** by caesium 137 throughout the protocol.

For each of these two studies, the three groups must include **an identical number of children and the breakdown in terms of age, sex and level of contamination by caesium 137 must be equivalent** for each group.

At the tend of the 3 weeks of treatment, each child will then benefit from all of the examinations described in paragraph 4.1.1 (anthroporadiametric measurements, electrocardiograms, cardiac ultrasonic scans, measurement of the levels of vitamins, measurement of the levels of minerals).

A comparison of the data acquired for each group of children and the cross-referencing of the results obtained over the course of the two studies described will then make it possible to rule on:

- The efficacy of apple pectin as a decorporating agent of caesium 137.
- The efficacy of pectin beyond any ingestion of foodstuffs contaminated by caesium 137.
- The relative efficacy of pectin compared to other substances entering in the composition of the mixture Vitapect®.
- The role of pectin on the evolution of the cardiovascular disorders observed.
- The consequences of an administration of pectin on vitamin and mineral balances.

4.2 Experimental research proposals

The proposals outlined in this paragraph concern **studies that could not be carried out on children,** either for practical feasibility reasons or for reasons of accessibility to the different biological samplings, or for ethical reasons. These studies must be carried out on an animal model, such as on rodents (rats, mice).

Their principal objective will be to clarify **the mechanisms behind the onset of any histological and functional abnormalities shown by the cardiac muscle following chronic contamination through ingestion of ^{137}Cs over several months.** Moreover, they should provide information with regard to **the distribution of caesium within the body.**

Two groups of animals will be constituted: the first will include rodents contaminated on a daily basis by foodstuffs containing ^{137}Cs over a period varying from 1 to 9 months and the second will include control rodents fed non contaminated food.

4.2.1 Protocol for studying the distribution of caesium in the body

The objective of the first part of the protocol will be to evaluate **the urinary and faecal excretions of caesium 137** throughout the experimentation. In order to overcome variations in these excretions throughout the day, samples will be taken over 48 hours, the animals then being placed in metabolism cages.

The second part of the protocol will have the objective of **measuring, after euthanasia of the animals, the concentration of caesium 137 in the blood, as well as in the thyroid, the adrenal glands, the pancreas, the thymus, the heart, the spleen, the liver and the kidneys.** The experiments will be repeated for different lengths of contamination in order to evaluate the evolution of the concentration of caesium in the different tissue compartments.

4.2.2 Protocol for studying the effects of caesium on the cardiac muscle

The experiments carried out on rodents will make it possible:

- To evaluate **any histological abnormalities of the myocardium** that could be caused by a chronic ingestion of caesium at low dose.
- To determine **if the contractile response of the heart to different agonists** (cholinergic, adrenergic analogues, etc.) **is modified** following these histological abnormalities.
- To determine **if the chronic ingestion of caesium can lead to modifications of the cardiac electrophysiology:** in fact, since caesium is an analogue of potassium, it would be pertinent to study the activity and the levels of genic and proteic expression of potassium carriers at the cardiac level (potassium canals, Na/K-ATPase pump, Na/K/2Cl co-carrier, etc.).

All of the results acquired in the course of the experimental studies will make it possible to apprehend in a satisfactory manner the mechanisms behind any deleterious effects of caesium on the heart and will thus provide the information required for a better understanding of the pathologies observed in children living in regions contaminated by caesium 137. Finally, these studies could be completed by protocols for administering pectin in contaminated rats if it turns out to be necessary to clarify the results obtained during the previously described clinical studies.

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