ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

HEALTH RISK ASSESSMENT OF EXPOSURE TO RACTOPAMINE THROUGH CONSUMPTION OF MEAT PRODUCTS

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Manuscript Info

Manuscript History:

Received: 15 July 2014
Final Accepted: 29 August 2014
Published Online: September 2014

Key words:
food safety, ractopamine residues, health risk assessment.

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Abstract

Background: This study aims to investigate health risk from ractopamine residues in food that is used as feed additive. Nowadays ractopamine is banned in 80 countries including European Union but at the same time 22 countries use it in swine breeding. Health risk assessment of veterinary drugs residues in food in particular within the World Trade Organization, the Eurasian Economic Community and the Eurasian Economic Community customs union is one of the priority areas in field of consumer health safety.

Findings: It was determined that using ractopamine MRL in animal food, recommended by CAC, carcinogenic risk level was 1.32×10^{-6} (acceptable risk). As a result of cardiovascular system disorders modeling, values of normalized risk have been obtained. Risk levels were unacceptable and could lead to life expectancy decrease due to additional cases of cardiovascular diseases (hypertensive diseases, ischemic heart diseases).

Conclusion: Consumption of food containing ractopamine on MRLs recommended by Codex Alimentarius Commission and even on ractopamine detection limit in meat products is prohibited because of ractopamine induced unacceptable health risk levels (cardiovascular functional disorders and cardiovascular diseases).

Introduction

Being admitted to WTO, Russia became its rightful member and started executing its undertaken commitments. One of the main WTO requirements, set by WTO member countries to the Russian Federation, is the fulfillment of the principles stated in WTO Agreement on Sanitary and Phytosanitary Measures. In accordance with WTO regulatory framework, it is necessary to have as the basis for sanitary measures the health risk assessment.

At its thirty-fifth session of the Codex Alimentarius Commission in a close call (69 votes for, 67 votes against, 7 abstainers), it was decided to adopt regulations on Maximum Residues Levels (MRLs) of ractopamine in certain tissues of pigs and cattle (CAC, 2012). To justify this decision, the analysis of the scientific evidence presented in the review of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (FAO / WHO, 2012) has been conducted. In accordance with the decision of Codex Alimentarius Commission, the MRLs for ractopamine in pork and beef have been set at 0.01 mg/kg, liver - 0.04 mg/kg, kidney - 0.09 mg/kg (CAC, 2012, FAO/WHO, 2010).

However, ractopamine is currently banned for use in fattening farm animals in 80 countries, including the European Union (EFSA, 2009, EC, 1996, Alemanno A. et al., 2012), but permitted for use in pig farming in 22 countries. Ractopamine is used in some countries as feed additive that stimulates the growth of muscles, reduces fat mass and increases feed efficiency in pigs, cattle, turkeys in doses of 5-20 mg/kg of feed stuff or improving bone carcass - 10-20 mg / kg of feed stuff.

The position of the Russian delegation, expressed at the 35th session of the Codex Alimentarius Commission, was that the acceptable daily intake of ractopamine was insufficiently substantiated and could not be used to

establish MRLs for ractopamine in meat and organ meat. The scientific justification for this position was the results of health risk assessment carried out by Rospotrebnadzor research organizations together with the RAMS Institute of Nutrition.

Ractopamine hydrochloride belongs to the class of phenylethanolamines. Pharmacologically, it is a beta-adrenergic agonist. Due to its physiological effect it is a stimulant, in the first place, of β2-adrenergic receptors located in the bronchi, skeletal muscle, heart, blood vessels, central nervous system, uterus and other organs. It has been defined, that the long-term use of beta-agonists drugs in therapeutic doses may cause the development of the following harmful effects: tachycardia, vasodilation, muscle tremors, nervousness, impaired metabolism, reducing the sensitivity of beta-adrenergic receptors. These effects are dose-related and pharmacologically predictable. Non-pharmacological effects include increased airway reactivity. However, the core group of adverse effects is considered to be cardiovascular system disorder.

Methods:

Health risk assessment associated with the presence of ractopamine residues in food, included four steps in accordance with the Principles and methods for the risk assessment of chemicals in food. Environmental Health Criteria 240 (WHO 2009):

– Hazard Identification. It determines specific risk factors in accordance with the principal exposure scenarios, possible violations of health-related risk factors, risk contingent;

– "Dose-Response" Assessment. It determines safe exposure levels for factors having threshold actions, and depending on parameterization "exposure - effect (response)" for the non-threshold factors;

– Exposure Assessment. It identifies and evaluates quantitative and qualitative terms, frequency, duration and route of exposure, using a scenario approach, taking into account the levels of product consumption (maximum, recommended, actual);

– Risk Characterization. It assumes a description of risks as the probability of individual effects with their quantitative characteristics, as well as evaluating the admissibility of risk level and its classification.

Ractopamine Hazard Identification is conducted on the basis of various studies' results available in scientific literature, including data on pharmacokinetics, biotransformation, acute and short-term toxicity, fetotoxicity, teratogenicity and genotoxicity, as well as the results of a limited number of studies conducted on humans.

The information about the development of uterine leiomyoma in the experiment on mice (Table 1) (WHO, 2004) was used as source information to form a model of "exposure – effect" relation and the risk level calculation. This also allowed us to assess health carcinogenic risk associated with ractopamine residues in food products at the level recommended by the CAC.

This information corresponds to the correlation between ractopamine exposure dose and cases of uterine hyperplasia in rats, described in formula 1:

$$R = a \cdot D, \quad (1)$$

where R – the number of uterine hyperplasia cases, D – ractopamine dose (mg/kg); a = 0.0011±0.000213 - model parameter.

With respect to non-cancer effects the "exposure – effect" correlation modelling has been carried out on the basis of data presented in FAO/WHO reports (WHO, 2004) and by the USA experts (Williams, 1987). As a basic model the evolutionary model of risk accumulation of cardiovascular system disorders was used, as described in the methodological recommendations "Quantitative non-cancer risk assessment due to exposure to chemical exposures on the basis of health risk evolutionary modelling" (Methodical recommendations 2.1.10.0062-12). When modelling, the risk accumulation recurrence correlation of functional cardiovascular system disorders is built:

$$R_{t+1} = R_t + (\alpha \cdot R_t + \beta \cdot D)C, \quad (2)$$

with specified initial risk value $R_{0,}$, where

R_{t+1} – risk of disorders at the moment $t+1$;

R_t – risk of disorders at the moment t;

α = 0.0835 - risk evolution coefficient based on natural causes,

β – ractopamine exposure coefficient,

C – interim empirical coefficient (for daily averaging (C=0,00274)),

D – ractopamine dose (mg/kg).

When building the recurrence relation of functional disorders risk accumulation for the cardiovascular system under ractopamine exposure through meat products, its toxicokinetics was taken into account (decrease of its content in body during a day by 85% (Elanco report #DO 4686, PO3086, and ABC-0330)) and the heart rate increase was considered as a marker effect.

The final form of the recurrence relation for the lower limit of ractopamine exposure on the cardiovascular system is represented by formula 3:

$$R_{t+1} = R_t + (0,0835 \cdot R_t + 0,191 \cdot 1,17 \cdot 0,15 \cdot D) \cdot 0,00274 \quad (3)$$

with the initial condition $R_0 = 0.001359$.

This recurrence relation is the basis for the construction of risk evolution curve of cardiovascular system disorders under the influence of ractopamine dose D (calculated risk) and the curve associated with it, excluding the ractopamine exposure (D = 0) (background risk).

The risk assessment is performed on the basis of the risk index calculation, given below:

$$\tilde{R}_t = \frac{\Delta R_t}{1 - R_t^{\hat{o}}} \quad (4)$$

The normalized risk index was scaled in value ranges:

0-0.05 - acceptable risk;

0.06-0.35 - moderate risk;

0.36-0.6 - high risk;

0.61-1 - very high risk.

Lifetime risk assessment was carried out for the time of ractopamine receipt t = 25550 hours, which corresponds to 70 years.

Non-cancer health risk assessment of ractopamine consumption with food products, was carried out for two scenarios: the ractopamine content in the amounts recommended by CAC as MPL (maximum permissible level), and at the limit of ractopamine quantitation in meat products.

To assess the Russian Federation population exposure to ractopamine, the data on food consumption in the Russian Federation in 2011 has been used (Results of household sample survey, 2012) (Table. 2).

Results:

Table 1. Background information for the modeling of carcinogenic risk associated with consumption of ractopamine residues with food products

Dose, mg/kg of weight per day	Number of mice in the experiment	Number of uterine leiomyoma cases	Probability of uterine leiomyoma development	Additional risk of uterine leiomyoma
0	60	1	0.016667	-
35	60	5	0.083333	0.066667
175	60	8	0.133333	0.116667
1085	60	10	0.166667	0.15

Table 2. Consumption of animal products in the Russian Federation

Food products	Daily consumption level, kg
Meat (muscle tissue)	0.222
Edible fats of animal origin	0.001

It was determined, that the pharmacodynamic effect of ractopamine in humans has been evaluated in a single study in young male volunteers, which resulted in determining NOEL - 67 μg/kg of body weight per day. Taken into account the administration of 50-fold safety factor the acceptable daily intake (ADI) was derived, which is equal to 1 μg/kg of body weight per day (EFSA, 2009, FAO / WHO, 2004).

Establishing the acceptable daily intake based on the results of this study has been criticized by the scientific institutions of the European Union, Russia and China. In particular, during the evaluation of materials, performed by the European Food Safety Authority (EFSA), the series of weaknesses in the justification of the ADI was found. Among other things, the results of some animal studies, in which it was not possible to observe no-effect level, were

not taken into account. Moreover, the unsatisfactory features of the study design, including its undercapacity, have been noted (EFSA, 2009).

Two scenarios of exposure have been considered. The first takes into account the permissible residue content of ractopamine at the level recommended by CAC, as well as the average consumption level of animal products by the population of the Russian Federation. In the second scenario the ractopamine intake at the lower limit of its quantitative determination in tissues (3-5 μg/kg (WHO, 2004)) was considered, with an average consumption level of animal products by the population of the Russian Federation.

The results of the ractopamine daily dose calculation for the selected scenarios are presented in Tables 3 and 4.

Table 3. Ractopamine dose calculation for Scenario 1

Product	Consumption, kg	Ractopamine content in the product, μg/kg	Ractopamine administration, μg	Dose, μg/kg of body weight
Meat	0.2216	10	2.216	0.0369
Edible fats	0.0008	10	0.008	0.0001
Total			2.224	0.0371

Table 4. Ractopamine dose calculation for Scenario 2

Product	Consumption, kg	Ractopamine content in the product, μg/kg	Ractopamine administration, μg	Dose, μg/kg of body weight
Meat	0.2216	3	0.664	0.011
Edible fats	0.0008	3	0.002	0.00004
Total			0.667	0.011

Thus, the average daily dose of ractopamine in the first scenario will be 0.371 μg/kg of body weight, in the second scenario - 0.011 μg/kg of body weight.

The calculation of the carcinogenic risk associated with the consumption of ractopamine dose with food products, recommended by CAC (1 μg/kg of body weight per day), showed that the level of 95% upper carcinogenic risk border will be $1.32 \cdot 10^{-6}$, what is classified as a level corresponding to the maximum permissible risk.

Non-cancer health risk assessment when exposed to ractopamine consumed with food products was carried out for two scenarios proposed in the phase of exposure evaluation. The results of additional risk evolution calculation in functional cardiovascular system disorders for two scenarios are presented in Table 5.

Table 5. Additional risk evolution in functional cardiovascular system disorders

Age, years	Additional risk	
	Scenario 1	Scenario 2
5	0.000	0.000
10	0.001	0.000
15	0.002	0.001
20	0.003	0.001
25	0.005	0.001
30	0.008	0.002
35	0.013	0.004
40	0.020	0.006
45	0.030	0.009
50	0.046	0.014

55	0.071	0.021
60	0.108	0.032
65	0.164	0.049
70	0.249	0.075
75	0.287	0.114

The results of the normalized risk index changes for two scenarios are presented in Table 6.

Table 6. Results of the normalized risk index changes

Age, years	Normalized risk index	
	Scenario 1	Scenario 2
5	0.000	0.000
10	0.001	0.000
15	0.002	0.001
20	0.003	0.001
25	0.005	0.002
30	0.008	0.002
35	0.013	0.004
40	0.020	0.006
45	0.032	0.010
50	0.051	0.015
55	0.082	0.024
60	0.135	0.041
65	0.237	0.071
70	0.470	0.141
75	1.000	0.396

The assessment of normalized risk index change for functional cardiovascular system disorders shows, that the unacceptable risk level would be formed in the case of ractopamine content in food products at the level recommended by CAC to the age of 25 years, at the limit of detiction – to the age of 40 years.

As a result of modelling of functional cardiovascular system disorders, it was found that in case of the first scenario the normalized risk of cardiovascular system disorders will be 0.47, which is classified as an unacceptable risk (Methodical recommendations 2.1.10.0062-12). This risk level may lead to the cardiovascular system additional diseases and reducing the projected life expectancy of the Russian Federation population.

As a result of the risk assessment according to the second scenario, the normalized risk of functional cardiovascular system disorders will be 0.141, which is also classified as an unacceptable risk (Methodical recommendations 2.1.10.0062-12). This risk level may also lead to the reduction in the projected life expectancy due to the cardiovascular system additional cases of disease (diseases characterized by high blood pressure, atherosclerotic heart disease).

The results of risk estimation for these scenarios are presented in Figures (1-3).

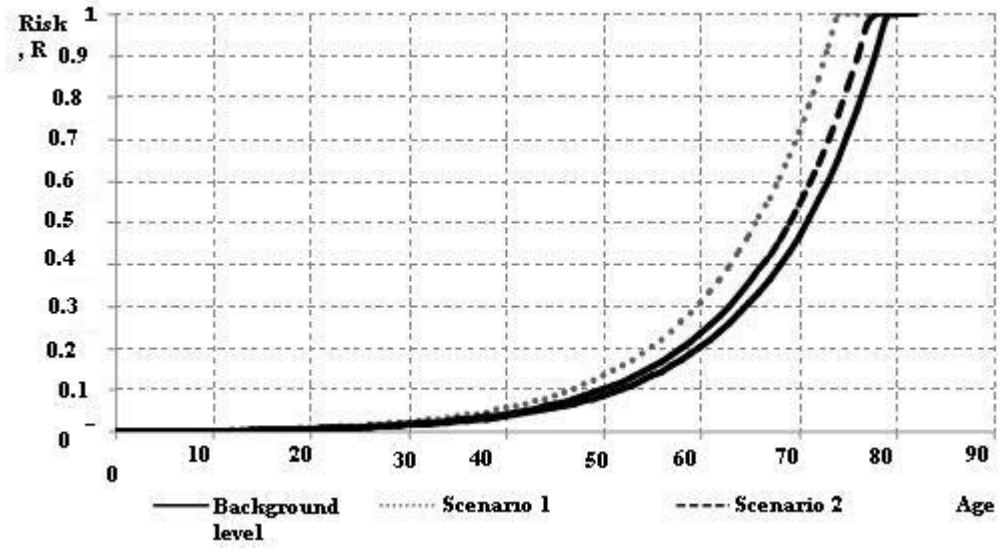

Fig. 1 Risk of cardiovascular system disorders

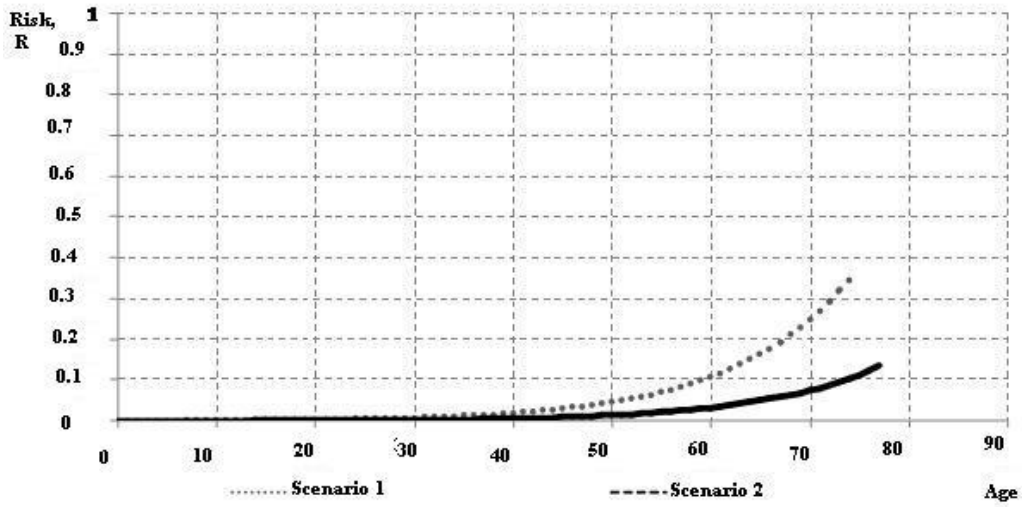

Figure 2: Additional risk of functional cardiovascular system disorders

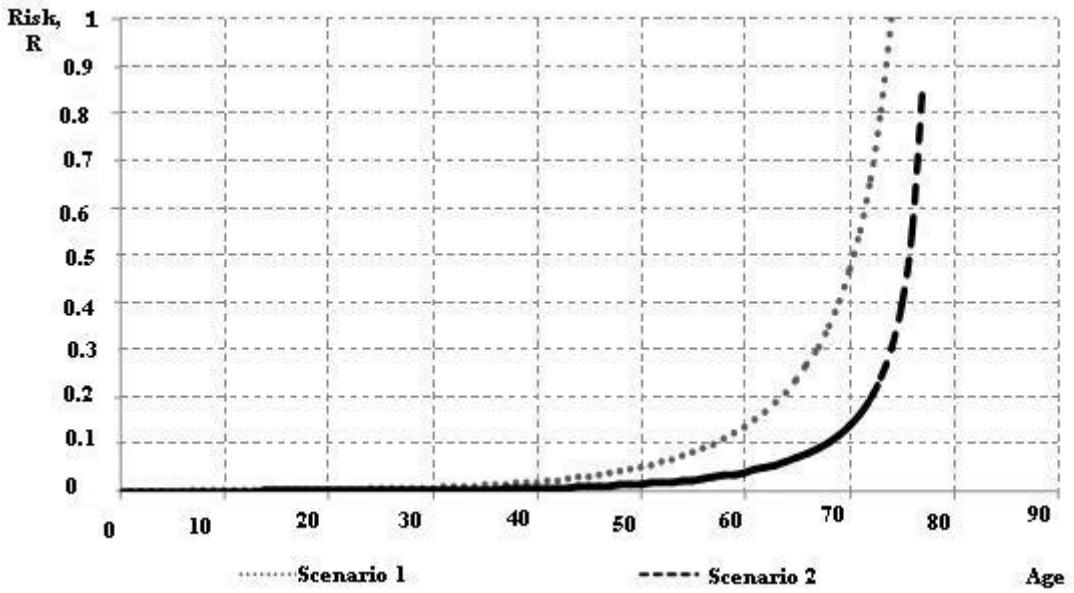

Figure 3: Normalized risk of cardiovascular system disorders

The important stage of this study was to evaluate the associated uncertainties. The uncertainties of risk assessment results should include not enough detailed information on the possible effects of chronic exposure to ractopamine on the human body, especially in the most sensitive groups of the population; uncertainties associated with the consumption of food; model uncertainties should also include a limited amount of research data. A number of uncertainties is caused by insufficient vision of the laws governing the formation of cardiovascular system functional disorders when exposed to ractopamine and related public health problems.

Conclusion:

Thus, it can be concluded that the assumed allowable daily dose of ractopamine proved inadequate and cannot be used to determine the maximum permissible levels of ractopamine in meat and its by-products. The maximum permissible levels of ractopamine in food products currently cannot be accepted in the Russian Federation and the consumption by the population of foods products containing ractopamine at these levels, and even at the levels of the detection limit in meat products, is intolerable because of an unacceptable risk of functional disorders and cardiovascular system diseases.

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