Philippine Journal of Science
151 (5): 1535-1555, October 2022
ISSN 0031 - 7683
Date Received: 06 Dec 2021

Risk Profiling of Beta-agonists in the Consumption of Pork by the Filipino Consuming Population

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Beta-agonists (β-agonists) are feed additives used in animal production (20–40 d before slaughter) to simultaneously reduce fat gain and increase the muscle mass of animals, but the residues may remain in the tissues of animals if the withdrawal period is not observed. This is a concern due to the potential adverse health effects to humans symptomized by increased heart rate, palpitations, vasodilation, and reflex tachycardia. This study described the potential risks associated with the consumption of pork with β-agonists to the Filipino pork-consuming population through the risk profiling process. Specifically, it consolidated the available information and determined the data gaps relevant to the risk profiling process, including available risk management options for β-agonist residues in pork. The study identified and characterized β-agonist as the hazard and pork as the concerned commodity. The risk was estimated through the evaluation of β-agonist residue concentrations in pork kidneys and pork meat from the National Veterinary Drug Residue Monitoring Program of the Philippine National Meat Inspection Service and the pork consumption data of the adult Filipino consuming population from the Department of Science and Technology–Food and Nutrition Research Institute in consideration of identified uncertainties, variabilities, and assumptions. The mean and maximum dietary exposures of the adult Filipino consuming population, with an assumed average body weight of Asian adults, to β-agonists in pork meat (0.0111 and 0.1478 µg/kg bw) and pork kidney (0.0166 and 0.4847 µg/kg bw) were estimated to exceed 100% of the acceptable daily intake of clenbuterol (0–0.004 µg/kg bw). These results indicate that there is an appreciable risk to the health of the Filipino population when it comes to the consumption of pork contaminated with β-agonists.

Keywords: beta-agonist, pork, dietary exposure, Philippines, risk profile

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INTRODUCTION

Risk profiling involves risk assessors and risk managers who will determine the need for a formal risk assessment and its extent through communication with other interested parties or stakeholders (WHO 2020). A risk profile contains information, including: [1] a brief description of the food safety problem, [2] the commodity or product involved and the pathways by which consumers may be exposed to the hazard, [3] possible effects or consequences of exposure to the society, [4] risk perception, [5] distribution of risks among different population sublevels, and [6] possible benefits regarding the use of the chemical in food (WHO 2020).

In the veterinary framework of food-producing animals, beta-agonists (β-agonists) are drugs utilized as repartitioning agents that signal the animal to add on lean muscle mass instead of fat (Landicho 2002; McCurry-Schmidt 2013). These drugs are usually administered at the end phase of the finishing period or 20–40 d before harvest date (4–6 mo after birth) since the animals become less efficient in transforming energy from feeds into muscles as they grow older (Chichester 2013). In this way, the decrease in fat content, increase in lean muscle mass, and increase in carcass weight of the animals will translate to both the increase in the economic value of the animal, as well as the net profit of the pig farmers (Chichester 2013; Jones 2014).

In 1999 and 2006, the US Food and Drug Administration (USFDA) approved the use of commonly used β-agonists such as ractopamine hydrochloride and zilpaterol hydrochloride, respectively, as feed additives (Beermann 2014) – as seen in Table 2. The former is usually used in cattle, swine, sheep, and turkey industries, whereas the latter is utilized just for cattle (Jones 2014; Beermann 2014). This approval has stirred a worldwide debate due to the lack of sufficient information regarding the potential side effects of β-agonist residues in food of animal origin when consumed by humans (Jones 2014). For instance, Chichester (2013) stated that there were no reports of foodborne illnesses or side effects experienced by humans with the addition of β-agonist in the diet of animals, which may be attributed to the short half-life of the drug, meaning that it is easily metabolized and excreted in the feces and urine of the animals and eventually lead to the depletion of β-agonist residues in the animal tissue or meat.

On the other hand, Zhu and co-authors (2019) reported that β-agonists are easily left in animal bodies and the consumption of contaminated meat has already led to food poisoning cases in humans. There have also been reports of β-agonist residues left in edible tissues in Hong Kong due to inappropriate usage of the drug in food-producing animal production (Hwang 2016). Studies focused on β-agonists show that since the drug in edible tissue is heat stable and can survive the temperature of boiling water, potential health concerns may arise such as nervousness, headache, tremor, dry mouth, body pains, and rapid or uneven heart rate (Hwang 2016). Cazzola and co-authors (2013) further reported that the main adverse effects of β-agonists in humans include increased heart rate, palpitations, vasodilation, and tachycardia, which can be especially dangerous for people with heart problems. These health concerns have caused many countries – led by China and the European Union (EU) – to ban the use of β-agonists in food animal products, even though approved by USFDA (Zhu *et al.* 2019).

Concern about the improper use of β-agonists in pork production in the Philippines was brought up by the Department of Agriculture–National Meat Inspection Service (DA-NMIS) due to consistent positive results in their monitoring program, despite the banning of certain β-agonists in the Philippines. Due to the potential adverse effects of β-agonist in humans as reported in several studies, it is beneficial to create a risk profile that can help risk managers in the decision-making process and proposal of mitigation measures.

This risk profile utilizes the risk assessment framework as described by the Codex Alimentarius Commission – which includes hazard identification, hazard characterization, exposure assessment, and risk characterization to identify the gaps needed to be addressed to be able to conduct a full-blown risk assessment.

There is only little local research and data available on the β-agonist dose-response studies, as well as its dietary exposure assessment in food. Moreover, there are no reports or proof of poisoning or illness due to exposure to β-agonists in the Philippines. These uncertainties are the data gaps that still need to be addressed or minimized to further the risk assessment and to come up with a more comprehensive risk estimate for the Filipino consuming population.

As such, this study sought to establish a profile on the risk of the consumption of pork potentially contaminated with beta-agonist (β-agonist) residues in the Filipino pork-consuming population. Through risk profiling, the study specifically aimed to address the following specific objectives based on formulated risk management questions:

1. to determine the data gaps in the risk profiling of β-agonist residues in the consumption of pork by the Filipino pork-consuming population;
2. to identify and characterize the food hazard (β-agonist) in the specific food commodity (pork) based on literature review;

Table 1. List of information needed to complete this risk profile, available information, and the gaps identified.

Needed information to complete the risk profile	Available information	Gaps identified
Hazard identification		
a. Sources of the hazard b. Hazard in the specified food	- Overseas studies regarding β-agonists in pork and other types of meat - Information on β-agonists from specialized agencies and organizations such as FAO/WHO and CAC, and government regulatory bodies such as USFDA, *etc.*	- Limited to no available published Philippine studies regarding the presence of β-agonists in pork in the Philippines - No clear definition in DA AO No. 14, Series of 2003, "Ban on the Use in Food Animals of Beta-agonist Drugs Used in Human as Bronchodilators and Tocolytic Agents" (DA-BAI 2003) of which compounds of veterinary drugs are considered banned in the Philippines ("such as but not limited to ...")
Hazard characterization		
a. Distribution and pharmacokinetics b. Adverse effects c. Dose-response d. Establishment of safe limits: Filipino adult consuming population e. Philippine reports of poisoning or illness	- Overseas studies on distribution and pharmacokinetics, and adverse health effects of β-agonists - Dose-response studies and HBGVs from JECFA online database on "Residues of some veterinary drugs in foods and animals" (FAO 2020)	- Limited to no available dose-response studies conducted in the Philippine context relevant to the consumption of pork contaminated with β-agonists - Limited, no recent, or no available reports of poisoning or illnesses directly associated with the consumption of pork contaminated with β-agonists in the Philippines
Exposure assessment		
a. Dietary hazard concentration in pork in the Philippines compared with overseas data b. Consumption information to establish baseline dietary exposure estimate c. Comparison of Philippine dietary exposures with overseas estimates d. Major contributing foods	- β-agonist residue concentration in pork meat and kidneys from the NVDRMP of NMIS using clenbuterol as the standard - Mean and percentile pork consumption of Filipino consumers by age or physiologic group from DOST-FNRI (pers. comm., DOST-FNRI 2020) - Average body weight of the Asian population from WHO (2009)	- No available disaggregated data from DOST-FNRI on the consumption of pork and data specific to sub-populations at risk - Available laboratory analyses for β-agonists are either sourced out to other countries or limited to the central office of the NMIS - No confirmatory test was done on the samples collected by NMIS - No monitoring using standards of other β-agonists such as ractopamine hydrochloride and zilpaterol hydrochloride - While monitoring data may be available, there is still a lack of data synthesis to determine the trend and therefore explore control options for non-conformities - Limited points in the food chain are analyzed for β-agonist residues in the Philippines - No Philippine data on dietary hazard concentrations of β-agonist residues in pork
Risk characterization		
a. Estimate of risk for the Philippines b. Adverse effects level applied to Philippine exposures c. Uncertainties, variabilities, and assumptions	- Estimated dietary exposures of the adult Filipino consuming population to β-agonist residues in pork meat and pork kidney - ADI of clenbuterol from JECFA online database on "Residues of some veterinary drugs in foods and animals" (FAO 2020) - Adverse health effects from various overseas studies - Existing control measures in the Philippines and overseas	- Lack of communication and participation between the national, regional, and provincial levels when it comes to control measures and the results of monitoring of NMIS

3. to estimate the dietary exposure and risk in the consumption of pork contaminated with β-agonist residues in pork based on identified uncertainties, variabilities, and assumptions; and
4. to determine the available risk management options for β-agonist residues in pork.

The risk profile was developed to serve as reference material for risk managers in evaluating risks to the Filipino consuming population and to aid in the decision-making and proposition of possible mitigation measures. This profile focuses on pork as the commodity and β-agonist residues as the hazard in the Philippines.

MATERIALS AND METHODS

The food hazard: commodity combination was identified and decided upon from the forum and discussion meetings with the DA-NMIS, which serves as the risk manager for meat safety, as it is the country's sole national controlling and competent authority on all matters of meat inspection and hygiene both for locally produced and imported meat (NMIS 2018).

The outline of this risk profile on β-agonist in pork in the Philippines was conceptualized in reference to CAC/GL 63-2007, CAC/GL 30-1999, Section III of the CAC Procedural Manual (FAO/WHO 2003), EHC 240: Principles for Risk Assessment of Chemicals in Food (WHO 2020), USDA/FSIS/2012-001 EPA/100/J12/001, and in consultation with an international food safety expert.

Phase 1: Determination of Data Gaps in the Risk Profiling of β-agonist Residues in the Consumption of Pork by the Filipino Pork-consuming Population

Risk profiling involves the consolidation of the available scientific information and the determination of the gaps in data needed to guide the risk managers in setting priorities and deciding on appropriate risk management actions. The study is primarily limited to the determination of the range of information needed to adequately reflect the Philippine scenario – specifically, pork produced in the Philippines and β-agonists as the specific hazard in the commodity.

This study reviewed literature covering scientific studies, standards, monitoring, evaluation, health risk assessment, reports of illnesses, and statistics regarding β-agonists in humans when used as feed additives in the animal production industry. The terms "beta-agonist," "veterinary drug," "ractopamine," "zilpaterol," "clenbuterol," "salbutamol," "meat," "swine," "pork," "risk assessment," "food safety," and "health risks" were used either individually or in combinations with each other to search online databases such as Google, Google Scholar, ScienceDirect, Wiley Online Library, ResearchGate, Taylor & Francis Online, Elsevier, National Center for Biotechnology Information, FAO/WHO Joint Expert Committee on Food Additives, Codex Alimentarius Commission, *etc.*, for literature dated from the year 2000 up to present. However, some works of literature from the 1980s and 1990s were also included due to the limited number of recent publications on the topic.

The reviewed literature was then tabulated to show the list of information needed to complete a risk profile or make a comprehensive decision based on a risk profile. Pertinent information relevant to the study of β-agonist in pork, which is not readily available and accessible in public domains, was requested from collaborating agencies and offices such as the NMIS and the Department of Science and Technology–Food and Nutrition Research Institute (DOST-FNRI) and were used in the estimation of dietary exposure and risk in this study.

Phase 2: Identification and Characterization of the Hazard (β-agonist)

The scoured literature was then organized and summarized into the following classifications: β-agonist (hazard), pork (commodity), and beta-agonist in pork (food hazard: commodity combination); these were used to present information about hazard identification and hazard characterization.

Hazard identification is defined by FAO/WHO (2003) as the identification of biological, chemical, and physical agents capable of causing adverse health effects and which may be present in a particular food or group of foods. Hazard identification includes the following: sources of the hazard and hazard in the specified food. Meanwhile, hazard characterization is defined by FAO/WHO (2003) as the qualitative and/or quantitative evaluation of the nature of the adverse health effects associated with biological, chemical, and physical agents that may be present in food. For chemical agents, a dose-response assessment should be performed. Hazard characterization includes the following: distribution and pharmacokinetics, adverse effects, dose-response, establishment of safe limits: Filipino adult consuming population, and Philippine reports of poisoning or illness.

Phase 3: Estimation of Dietary Exposure and Risk Based on Uncertainties, Variabilities, and Assumptions

The overall degree of confidence in the dietary exposure and risk estimates was discussed based on uncertainties and variabilities formulated as assumptions in the Philippine scenario. Uncertainties are the data gaps

needed to be addressed or minimized to further the risk assessment and to come up with a more comprehensive risk estimate for the Filipino pork-consuming population. Meanwhile, the variabilities are the information used in risk profiling that is constantly varying and cannot be represented by a single value but can be addressed with precision (FAO 1995).

Data gathering and analysis. The raw data on β-agonist residue concentrations in different foods of animal origin from 2015–2019 was acquired through the National Veterinary Drug Residue Monitoring Program (NVDRMP) of the NMIS. The NVDRMP of NMIS conducted screening test methods in meat samples, urine, and other edible tissues such as kidneys and liver from several commodities in the initial monitoring of tissue samples for β-agonists in 2015, and these included beef, chicken, crocodile, and pork, following a randomized sampling and testing schedule spread throughout the entire year (Nones 2015). However, based on the initial results, the monitoring for 2016–2019 focused on pork kidneys only.

The screening test for β-agonist residues utilized Randox Laboratories Ltd. evidence investigator Growth Promoter Multiple Matrix screen kit EV3726 with analyte standardized to clenbuterol has a limit of detection (LOD) of 0.2 µg/kg. The lower-, middle-, and upper-bound mean of β-agonist residue levels in pork kidney (n = 1933) and pork meat (n = 35) samples collected were calculated by setting the non-detected samples to values of zero (0), LOD/2 = 0.1 µg/kg, and LOD = 0.2 µg/kg, respectively, and then getting the mean of each data set, based on the Environmental Health Criteria 240: Principles and Methods for the Risk Assessment of Chemicals in Food of the WHO (2020).

The calculated mean β-agonist residue levels in pork in the Philippines were then compared with overseas data obtained through the review of related literature regarding β-agonist residue levels in other countries.

On the other hand, local food consumption data for pork and other pork products in 2013 were acquired through a memorandum of understanding with the DOST-FNRI (notarized 2020, pers. comm.) to establish the baseline dietary exposure estimate of Filipinos. The data were categorized into physiologic age groups with their respective means and percentile consumption.

Estimation of dietary exposure and risk. The dietary exposure was estimated and calculated using the equation provided by FAO/WHO (2011):

$$Dietary\ exposure = \frac{(Concentration\ of\ chemical\ in\ food\ x\ Food\ consumption}{Body\ weight} \quad (1)$$

The estimated dietary exposure of the Filipino adult consuming population was calculated using the following information: [1] lower-bound mean and maximum levels of β-agonist residues (WHO 2020), [2] the 97.5th percentile daily pork consumption value of the adult Filipino consuming population (DOST-FNRI 2020, pers. comm.), and [3] an assumed average weight of 55.0 kg for Asian adults (WHO 2020). However, it is important to note that the consumption levels for both pork kidneys and pork meat were assumed to be the same due to the lack of disaggregated data on pork consumption.

Phase 4: Determination of Available Risk Management Options for β-agonists in Pork

The information on the available risk management options for β-agonist in pork from gathered and reviewed literature discussed the existing control measures in the Philippines: regulatory and advisory, control measures employed overseas, and control options.

RESULTS AND DISCUSSION

Phase 1: Data Gaps in Profiling the Risk of β-agonists in the Consumption of Pork by the Filipino Pork-consuming Population

Table 2 shows the list of information needed to complete this risk profile or make a comprehensive decision based on a risk profile. It also details which information is

Table 2. USFDA-approved β-agonists for food-producing animal production (Beermann 2014).

β-agonists	Manufacturer	Brand name	Date of approval	Food-producing animal
Ractopamine hydrochloride	Elanco Animal Health, Indianapolis, IN, USA	Paylean®	Dec 1999	Swine
		Optaflexx®	Jun 2003	Beef cattle
		Topmax™	Apr 2009	Turkey
Zilpaterol hydrochloride	Merck Animal Health, Whitehouse Station, New Jersey, USA	Zilmax®	2006	Beef cattle

readily available and which is still lacking, especially in the Philippine context. In identifying the gaps, the risk managers (*i.e.* NMIS) are also presented with options for their further action.

Phase 2: Identification and Characterization of the Hazard (β-agonist)

β-agonists are a family of naturally occurring and synthetic organic phenylethanolamine compounds that are employed in the livestock industry (particularly for pigs and ruminants such as beef cattle) to improve growth rate and feed conversion ratio and reduce carcass fat and increase muscle mass (Qiang *et al.* 2007; Beermann 2014).

β-agonists such as clenbuterol, salbutamol, and ractopamine have been studied and evaluated for their potential muscle growth enhancement and anti-obesity effects to promote or improve feed efficiency and achieve higher muscle-to-fat ratios in farm animals (Beermann 2014). Even though the results show that all have beneficial effects that increase muscle growth rate and decrease the fat content of animals, only ractopamine and zilpaterol were approved for use in the food-producing animal production industry (Beermann 2014).

The presence of β-agonists in animal tissues can cause acute poisoning when consumed by humans – particularly when consumers have a history of muscular tremors, cardiac palpitation, muscular pain, headache, dizziness, nausea, vomiting, fever, and chills (Brambilla *et al.* 2000). As a result, the use of β-agonists in animal feeds has been banned in many countries, however, illegal use of β-agonists in animal feeds still occurs in many countries (Brambilla *et al.* 2003; Centner *et al.* 2014).

Identification: sources of the hazard. In the production of food-producing animals, β-agonists are used in the growth promotion of animals mainly to increase their lean muscle mass (USDA-FSIS 2018). These are USFDA-approved feed additives, which not only act to enhance lean muscle mass but also to increase both the growth rate and feed efficiency of the animal, which in turn adds to the economic value of the animals (Chichester 2013).

According to Landicho (2002), β-agonists act as repartitioning agents as they simultaneously reduce fat accumulation and promote an increase in lean muscle mass in growing animals. Repartitioning starts when β-agonists bind to beta-adrenergic receptors located on skeletal muscles and adipose cell membranes (Dilger 2015). The magnitudes of changes experienced when β-agonists are fed to animals are considered dependent on the dose and the length of time, for which the β-agonists are consumed so the changes that occur in animal cells due to the consumption of β-agonists are not progressive nor continue to affect over long periods (Beermann 2014). Additionally, the animals become less efficient in repartitioning energy into muscles as they grow older (McCurry-Schmidt 2013). These are the reasons why the recommended time of adding β-agonists to feeds is at the end of the finishing period or around 20–40 d before the harvest date (Chichester 2013).

In adipose cell membranes, biochemical signals are sent throughout a complex mechanism that involves consequent activation of associated enzymes, which eventually leads to the following: [a] decreased rates of both fat synthesis and storage (lipogenesis), and [b] increased rates of fat mobilization from the cell (lipolysis) (Muir 1988; Beermann 2014; Johnson *et al.* 2014).

In skeletal muscles – otherwise known as muscle fibers – the signaling pathways include an increased rate of ribonucleic acid synthesis, which in turn leads to an increased rate of muscle protein synthesis in cells (Muir 1988; Beermann 2014; Johnson *et al.* 2014). This phenomenon is known as muscle hypertrophy or an increase in muscle cell size without an increase in cell number (Beermann 2014).

In the same regard, the USFDA (2019a) has approved the use of some hormone implants such as natural estrogen, progesterone testosterone, and their synthetic derivatives to increase the growth rate and feed efficiency of animals, particularly cattle and sheep. β-agonists, unlike hormone implants, do not affect the hormone status of the animal since it only binds to cell receptors to stimulate protein synthesis and suppress protein degradation, both of which contribute to the growth in the size of animal muscle fibers (USFDA 2019a).

As of 2014, there are only four branded β-agonist feed additives approved by the USFDA (Prestegaard 2014; Beermann 2014). Table 2 shows the approved products, their manufacturer, brand name, date of approval, and application to the food-producing animal industry.

Ractopamine hydrochloride is the only β-agonist approved by the USFDA as a feed additive for swine in the US. The USFDA (2019b) has approved the ractopamine dosage range of 4.5–9 g/ton of complete feed for pigs heavier than 150 lb (for the 45–90 lb of weight gain before slaughter). This translates to 5–10 mg/kg of diet or a concentration of 5–10 ppm (Storlie 2012). According to Meat+Poultry (2015), approval by the USFDA for use of β-agonists (particularly ractopamine) is also applicable in 25 other countries – including Australia, Brazil, Canada, Indonesia, South Korea, Mexico, Thailand, and the Philippines. In the Philippines, ractopamine hydrochloride can reportedly increase the protein content by 24% and decrease fat by 34% by just incorporating it at the rate of 10–20 ppm into complete feeds during the last 40 kg of live weight gain (Plaridel Products and Services, Inc. 2019).

It was estimated in the US that about 60–80% of cattle are fed with either zilpaterol hydrochloride or ractopamine hydrochloride (Chichester 2013). Beermann (2014) reported that when zilpaterol hydrochloride and ractopamine hydrochloride are fed as guided by the manufacturers for the last 20 and 42 d before harvest, respectively, there were significant increases in both carcass weight and lean meat yield in beef. Other β-agonists that have been involved in experiments regarding various human and animal medical conditions but are not labeled for use as feed additives include cimaterol, R-salbutamol, and clenbuterol (AVMA 2014). Consequently, these drugs cannot be used commercially while ractopamine and zilpaterol are typically added to livestock feed in the final weeks before slaughter (Beermann 2014). With the addition of β-agonists in the diet of the animals fed in the US, there have been no reports of foodborne illnesses or side effects in humans arising from the drugs. This may be attributed to the very short half-life of the β-agonists (2–34 h), which translates to the fast breakdown, metabolism, and excretion through the feces and urine, of the drugs by the animal's organs. Consequently, this results in no β-agonist residues found or stored in the animal's tissues (*i.e.* meat) that is usually consumed by the consumers (Chichester 2013).

Nonetheless, the approval of the use of β-agonists as feed additives has caused a worldwide debate due to the potential negative health effects of consuming meat products with β-agonist residues. Human health concerns regarding β-agonist residues are based on the lack of sufficient information (Jones 2014). This has led to 160 countries – particularly the EU, China, and Taiwan – either restricting or banning imported meats with traces of β-agonists, specifically ractopamine (Jones 2014; Wood *et al.* 2010). Currently, β-agonists used as bronchodilators and tocolytic agents in humans are part of the list of drugs banned for use in food animals in the Philippines together with chloramphenicol, nitrofurans, diethylstilbestrol, olaquindox, and carbadox (NMIS 2017).

Identification: hazard in the specific food. Meat is considered to have a major contribution to the human diet in terms of its protein, fat, inorganic salts, and vitamins, and the main source of meat is animal farming (Xu *et al.* 2019). Since consumer demand for high-quality lean meat is continuously increasing worldwide, the pig farming industry has strived to maximize its efficiency and productivity in terms of existing farm practices (Luk 2018). One of the options in doing this is the inclusion of growth-promoting agents in animal feeds, such as hormones, antibiotics, and β-agonists (Luk 2018).

β-agonists have been used since the 1980s legally and illegally as smooth muscle relaxants for bronchodilation cases (Cheng *et al.* 2016). However, since β-agonists are known to promote lean muscle growth in animals, hence increased profits, its misuse in food animals has been widely reported worldwide and has led to its banning in some countries due to its adverse effects on humans (Cheng *et al.* 2016). Some of the often-used β-agonists that promote higher fat-to-muscle ratios in farm animals are clenbuterol, salbutamol, and ractopamine (Xu *et al.* 2019).

Clenbuterol has been used illegally as a growth-enhancing agent, primarily in cattle, and is administered up to the time of slaughter (Sumano *et al.* 2002). Residue studies and results of regulatory monitoring indicate that clenbuterol residues are likely to be in excess of the maximum residue limits (MRL), particularly in the liver. Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1996 recommended that clenbuterol should not be used as a growth-enhancing agent due to potential abuse but can be applicable for nationally approved therapeutic uses such as tocolysis or as an adjunct therapy for respiratory diseases (FAO 2020).

Xiong and co-authors (2006) conducted a study focusing on the effect of dietary ractopamine, a β-agonist, on the tenderness and post-mortem protein degradation of pork muscle. Twenty-four (24) finishing pigs with a starting weight of 82 kg were divided into two groups and then into each was introduced to a distinct dietary regimen with the first group consuming a corn-soybean meal basal diet, whereas the second group ate the basal diet with added 20 ppm ractopamine hydrochloride. Xiong and co-authors (2006) reported that ractopamine-supplemented feeding increased both the pig carcass weight and the lean muscle percentage. Additionally, the results showed that ractopamine-fed pigs exhibited a slower rate of protein degradation relative to the control group.

Yodrasing and co-authors (2015) analyzed 74 samples of swine, cattle, and chicken feeds in Thailand for three β-agonists (salbutamol, clenbuterol, and ractopamine). While β-agonist contamination was found most frequently in cattle feed (91%), 69% of swine feeds contained β-agonists. The study detected high concentrations of clenbuterol in all feed samples, especially in swine feeds that recorded 0.35–3.94 ng/g. They concluded that the illegal usage of these substances may harm animals, humans, and the environment.

Another study by Noppon and Noimay (2012) monitored β-agonist residues in 261 swine tissues from northeastern Thailand. The overall detection rates were 91.95% or 240 of the 261 samples, with a cut-off value of 2 ng/mL for the residue limit. The results showed a significant difference in the mean concentration of β-agonist residues in swine liver and swine meat, with respective values of 0.123 and 0.061 ng/mL. Additionally, the range of detections was between 0.000–0.469 and 0.000–0.196 ng/mL for swine

liver and swine meat, respectively. Nonetheless, it was concluded by Noppon and Noimay (2012) that all the samples were safe for consumption when compared to a previous concentration report of 2.7 ng/mL, as well as 1.00-9.00 ng/g in Malaysia.

A study conducted in Thailand by Hung and co-authors (2010) reported that the highest concentrations of salbutamol found in the liver, kidney, lung, heart, brain, and muscle of pigs administered with 3 ppm salbutamol for 14 d were 70.42, 31.88, 26.06, 6.76, 3.41, and 2.97 ng/g, respectively. Additionally, the stomach and large intestine retained salbutamol residues for a prolonged time (11 d) compared to the liver, lungs, brain (4 d), and other tissues (2 d).

In another study by Pleadin and co-authors (2010), 20 µg/kg of clenbuterol per body mass of pig per day was administered for 28 d, and it was reported that the highest clenbuterol content in the muscle of treated animals was recorded on Day 0 of treatment (4.40 ± 0.37 ng/g). This significantly exceeded the MRL of 0.1 ng/g. Only on Day 7 of withdrawal did it reach the MRL at around 0.10 ± 0.02 ng/g and on Day 14 of withdrawal, the clenbuterol content was below the LOD (0.1 ng/g) in all samples. It was stated that the administration of clenbuterol as a growth promoter in pig production could lead to residues in meat for human consumption up to 7 d after treatment discontinuation.

Lastly, in a study made by Cheng and co-authors (2016), the urinary concentrations of the β-agonists ractopamine and zilpaterol were quantified using LC-MS/MS from urine samples of US breast cancer and lung cancer patients (n = 370). Results show that among all urine samples, 8.1% had ractopamine concentrations in between the LOD and LOQ, but none had ractopamine concentrations above the LOQ. In the case of zilpaterol, 1.9% of the samples had concentrations between the LOD and LOQ, and 1.1% had concentrations above LOQ with a calculated mean concentration of 0.07 ng/mL. Moreover, detectable urinary concentrations of zilpaterol were observed more among patients with higher meat intake levels, relative to those with lower consumption. They emphasized that since both ractopamine and zilpaterol are not used in human medicine nor are generally available to US consumers, the exposure can only be accounted for through the consumption of meat.

Characterization: distribution and pharmacokinetics. β-agonists help regulate the flow of air into the lungs by first binding with the β-receptors located on these muscles, then undergoing a complex pathway involving consequent activations of associated enzymes, and finally leading to the relaxation of airway smooth muscles (Amrani and Panettieri 2003; Cazzola *et al.* 2013). Besides their effects on airway smooth muscles, β-agonists also bind and have vital functions on cardiac smooth muscle, liver, and kidneys. Some of the overall effects are [1] inhibitory action on ASM; [2] stimulation of the cardiac muscle, resulting in increased heart rate (contractility, conduction velocity, relaxation); [3] inhibition of mediator release from mast cells; [4] metabolic actions (*e.g.* glycogenolysis in liver and skeletal muscle, increasing glucose); [5] endocrine actions (increase in insulin and release of glucagon); and [6] prejunctional action on parasympathetic ganglia, that increases or decreases acetylcholine release (Cazzola *et al.* 2013; Hsu and Bajaj 2019).

Different compounds under the group of β-agonists are generally well-absorbed immediately from the gastrointestinal tract. The excretion, absorption, bioavailability, and half-lives in plasma of various radiolabeled β-agonists are presented in the following table, as summarized by Ungemach (2004).

As seen in Table 3, clenbuterol has a higher general bioavailability in both plasma and urine after oral

Table 3. Results of various absorption and excretion studies of radiolabeled β-agonists in humans (Ungemach 2004).

Compound	Species	Excretion and absorption [a]		Bioavailability (% of parent drug)		Half-lives in plasma (h)
		Time (h)	Percentage of dose (%)	Plasma[b]	Urine[c]	
Clenbuterol	Human	96	80 (U)	75[d]	66.4 [d]	30–33.9
Ractopamine	Human	24	> 46 (U)	–	2 [d]	3.9
Salbutamol	Human	72	76 (U)	20 [d] oral	< 30 [d]	2–3.9
Terbutaline	Human	72	40 (U)	15 [d] (oral)	6 [d]	11–18
				> 50[e]	60 [e]	

[a]Apparent absorption expressed as a percentage of the orally administered dose excreted in urine (U) at the indicated time (h) after dosing
[b]Percentage of radioactivity in plasma represented by the parent drug, generally measured at peak concentration in the plasma or serum
[c]Percentage of radioactivity in urine represented by the parent drug
[d]Oral
[e]Intravenous

administration compared to the other specified β-agonists. Moreover, clenbuterol has been reported to have an extended plasma half-life relative to the low to negligible binding of other β-agonists to plasma proteins. These may be attributed to the higher remaining quantity of the parent drug and slower elimination rate of clenbuterol in animal tissues compared to other β-agonists (Ungemach 2004). It must also be noted that the β-agonists bioavailability, such as that of terbutaline, is generally greater when administered intravenously, rather than orally. According to Ungemach (2004), this data suggests that in oral administration of β-agonists, there must be a significant first-pass metabolism that happens in the intestine and liver but the general excretion of oral and/or intravenous β-agonists for most species is predominantly through the urinary system and is completed in about 48 h.

Characterization: adverse effects. There have been numerous incidences of acute food poisoning due to the consumption of meat products tainted with β-agonists such as clenbuterol, salbutamol, terbutaline, and ractopamine (Xu *et al.* 2019; Hung *et al.* 2010). Some of the specified main adverse effects of acute β-agonists poisoning on humans are increased heart rate, palpitations, vasodilation (decrease in blood pressure), and reflex tachycardia (condition when the heart beats more than 100 times per min) (Cazzola *et al.* 2013; Billington *et al.* 2017). These effects usually happen when β-agonists provoke β-adrenoreceptors in the atria and ventricles resulting in indirect stimulation of the heart muscle (Cazzola *et al.* 2013; Billington *et al.* 2017). Other reported symptoms include dizziness, nausea, vomiting, chest tightness, anxiety, shaking, weakness, and instability (Noppon and Noimay 2012). Patients with heart disorders, high blood pressure, diabetes, epilepsy, and hyperthyroidism are considered to be the vulnerable population due to the adverse effects of excess β-agonist exposure through consumption (Luk 2018; Noppon and Noimay 2012).

Table 4 below shows the summarized cases of human intoxication with residues of the β-agonist clenbuterol, as reported by Kuiper and co-authors (1998).

In Hong Kong, it has been reported that inappropriate usage of β-agonists in food-producing animal production may lead to residues left in edible tissues that may be eaten by consumers, making it a significant health concern (Luk 2018). Moreover, clenbuterol in edible tissues is heat-stable, meaning that common cooking methods such as frying, roasting, and boiling will not eliminate the said residues (Luk 2018).

Relative to clenbuterol, ractopamine, and zilpaterol have lower bioavailability and potency and have shorter plasma half-lives (Cheng *et al.* 2016). Nonetheless, adverse

Table 4. Cases of human intoxication with residues of clenbuterol (Kuiper *et al.* 1998).

Place	Period	Suspected food	Number of cases	Remarks
Central Spain	Oct 1989– Jul 1990	Cow liver	135 persons (43 families)	• Symptoms appeared 0.5 to 6 h after ingestion up to ~ 40 h • Residue concentration: 160-291 µg/kg liver
Northern Spain	Jan 1992–Apr 1992	Veal liver, tongue, or cannelloni	232 cases	• Symptoms include tachycardia, muscle tremors, nervousness, myalgia, and headache • Symptoms appeared 15 min to 6 h after consumption up to ~ 6 d • Residue concentration in urine: 11–486 µg/L (n = 47)
Barcelona, Spain	1992	Veal liver	15 cases	• Clenbuterol concentration from one slaughterhouse: 19–5,395 µg/kg liver (n = 9)
France	1990	Veal liver	22 persons	• Symptoms appeared 1–3 h after consumption • Patients recovered within 1–3 d • A woman with a history of heart disease developed marked palpitations, whereas her son did not (may indicate people with heart conditions as a more vulnerable population) • Clenbuterol concentration: 375–500 µg/kg liver

side effects on humans have been associated with the consumption of these β-agonist residues in cattle and swine meat. Among the expected public health effects of these include cardiotoxicity, promotion of certain tumor growth and cell proliferation in the human body, and even mortality (Cheng *et al.* 2016).

In Taiwan, it was announced by their Council of Agriculture in 2006 that "the manufacture, prescription, import, export, sale, display of, or administration to food-producing animals of β-agonists including salbutamol, terbutaline, clenbuterol, and ractopamine is prohibited" due to their side effects to humans such as slight skeletal muscle tremors in the hands, an increase in heart rate because of peripheral blood vessel dilation, high blood sugar, headaches, and stress (Lee *et al.* 2017).

Characterization: dose-response studies for β-agonists in humans. Table 5 summarizes the recommendations of the JECFA as reported in the online database on "Residues of some veterinary drugs in foods and animals" based on dose-response studies for β-agonists such as clenbuterol, ractopamine hydrochloride, and zilpaterol hydrochloride in humans (FAO 2020).

Characterization: establishment of safe limits for β-agonists residues in general population. Regulations have either not set an MRL or have a zero-tolerance level for β-agonists. As reported in the JECFA online database on "Residues of some veterinary drugs in foods and animals" (FAO 2020), the committee has established limits for acceptable daily intake (ADI) and MRLs for clenbuterol, ractopamine hydrochloride, and zilpaterol hydrochloride, as summarized in Table 6.

Characterization: Philippine reports of poisoning or illness. No reports of poisoning or illness due to exposure to β-agonists in food-producing animals in the Philippines were found. Meanwhile, the results of sample analyses and survey responses were utilized in the subsections on exposure assessment and risk characterization.

Phase 3: Estimation of Dietary Exposure and Risk Based on Uncertainties, Variabilities, and Assumptions

Dietary hazard concentrations of Beta-agonists in pork in the Philippines compared with overseas data. Table 7 shows the summary of the calculated concentrations of β-agonists in pork kidney (n = 1933) and pork meat (n = 35) samples from the 2015–2019 NVDRMP of the DA-NMIS.

Table 8 presents the residue levels of various β-agonist compounds in numerous animal species currently available in various literature. Comparing these amounts with the levels presented in Table 7, it is noticeable that the β-agonist residue levels in pork samples in the Philippines are higher than in other Asian countries.

Consumption information to establish baseline dietary exposure estimates. According to Pork Checkoff (2017), pork is the most consumed meat globally in 2016 with a percentage of 40.4%, compared to chicken (32.4%), beef (21.8%), and mutton and goat (5.3%). Similarly, in 2015, pork is also the most consumed meat in the Philippines (DOST-FNRI 2016), and the top five pork-consuming regions are Cagayan Valley (14.034 kg/yr), National Capital Region (13.626 kg/yr), Cordillera Administrative Region (13.388 kg/yr), Central Luzon (12.445 kg/yr), and Ilocos Region (12.705 kg/yr) (PSA 2017). Table 9 presents the mean and percentile pork consumption of Filipino consumers only by age or physiologic group in 2013 (DOST-FNRI 2020, pers. comm.).

Dietary exposure assessment of β-agonists in the consumption of pork in the Philippines. The following are the three factors that were considered to assess the dietary exposure or the amount of chemical ingested *via* food to β-agonist: [1] the chemical concentration or amount of chemical in food, [2] the consumption or amount of food consumed, and [3] the average body weight of the population (kg). The dietary exposure was estimated and calculated using Equation 1.

Table 5. Dose-response studies on β-agonists as reported by JECFA (FAO 2020).

	NOEL [a] (μg/kg bw)	LOAEL [b] (μg/kg bw)	Species	Evaluation year
Clenbuterol[c]	0.04	–	Human	1998
Ractopamine hydrochloride[c]	67	–	Human	2006
Zilpaterol hydrochloride[c]	–	0.76	Human	2015

[a]"NOEL" – no observable effect level; based on therapeutic or bronchodilator effect
[b]"LOAEL" – lowest observable adverse effect level
[c]JECFA online database on "Residues of some veterinary drugs in foods and animals" (FAO 2020)

Table 6. Acceptable daily intake (ADI) of some β-agonists and maximum residue limits (MRL) in animal tissues (FAO 2020).

Beta-agonist	ADI [a] (µg/kg bw)	Species	Tissue	MRL [b] (µg/kg)
Clenbuterol[c]	0–0.004	Cattle	Kidney	0.6
			Liver	0.6
			Muscle	0.2
			Milk	0.05
			Fat	0.2
		Horse	Fat	0.2
			Liver	0.6
			Muscle	0.2
			Kidney	0.6
Ractopamine hydrochloride[c]	0–1	Cattle	Fat	10
			Muscle	10
			Kidney	90
			Liver	40
		Pig	Liver	40
			Skin + Fat	10
			Kidney	90
			Muscle	10
Zilpaterol hydrochloride[c]	0–0.04	Cattle	Kidney	3.3
			Liver	3.5
			Muscle	0.5

[a]"ADI" – acceptable daily intake
[b]"MRL" – maximum residue limit
[c]JECFA online database on "Residues of some veterinary drugs in foods and animals" (FAO 2020)

Table 7. β-agonist residue levels (µg/kg) in pork kidney and meat samples in the Philippines collected by the NVDRMP of the NMIS from 2015–2019.

	β-agonist residue levels in kidneys (µg/kg)			**β-agonist residue levels in meat** (µg/kg)		
	Lower- bound [a]	Middle- bound [b]	Upper- bound [c]	Lower- bound [a]	Middle- bound [b]	Upper- bound [c]
Mean	2.30	2.37	2.44	1.55	1.63	1.70
Median	0.00	0.10	0.20	0.00	0.10	0.20
Maximum	67.28	67.28	67.28	20.52	20.52	20.52
Standard deviation	6.19	6.16	6.14	3.88	3.85	3.82

*Screening test using Randox Laboratories Ltd evidence investigator Growth Promoter Multiple Matrix screen kit EV3726 with analyte standardized to clenbuterol (LOD = 0.2 µg/kg)
[a]Non-detected samples set to a value of 0
[b]Non-detected samples set to LOD/2 = 0.1 µg/kg
[c]Non-detected samples set to LOD = 0.2 µg/kg

Table 8. β-agonist residue levels of different commodities and sample types in other countries.

Target compound	Target species	Sample type	Amount of residue	Reference
–	Goat Cattle Swine	Liver Muscle	1.00–9.00 ng/g	Noppon and Noimay (2012)
–	–	–	2.7 ng/ml	
Clenbuterol	Swine	Liver Muscle	0.123 ng/ml 0.061 ng/ml	
Clenbuterol	Swine	Ribs Loin Internal organs	1.06 µg/kg 0.85 µg/kg 0.95 µg/kg	Xu *et al.* (2019)
Ractopamine	Swine	Ribs Loin Internal organs	0.90 µg/kg 0.67 µg/kg 0.90 µg/kg	
Salbutamol	Swine	Ribs Loin Internal organs	0.69 µg/kg 1.93 µg/kg 0.71 µg/kg	

[a]Found in Noppon and Noimay (2012)

Table 9. Mean and percentile pork (fresh and cooked) intakes in the edible portion in grams of consumers only by age/physiologic group in 2013 (pers. comm., DOST-FNRI 2020).

Age/ physiologic group	Mean (g)	Percentile (g)								
		2.5	5	10	25	50	75	90	95	97.5
6 mo–5 yr	47.5	5.6	8.2	11.0	18.7	35.8	61.0	102.6	134.5	173.5
6–12 yr	77.4	9.5	13.1	18.7	34.5	58.4	97.0	159.5	213.2	268.7
13–19 yr	103.3	10.2	15.1	22.4	39.9	79.7	135.1	216.5	284.3	342.3
20–59 yr	111.1	10.1	15.1	22.3	39.9	79.7	142.3	233.8	303.5	396.2
60 yr & above	83.4	9.7	12.5	17.3	34.5	66.9	110.5	171.3	213.4	291.9
Pregnant	88.7	9.7	13.4	23.4	39.9	74.0	116.8	192.6	241.3	273.6
Lactating	99.9	9.9	12.1	18.2	36.3	72.3	134.5	210.9	290.7	372.7

The estimated dietary exposure of the Filipino adult consuming population, as presented in Table 10, was calculated using the following information: [1] lower-bound mean and maximum levels of β-agonist residues (WHO 2009), as presented in Table 7; [2] the 97.5th percentile daily pork consumption level of the adult Filipino consuming population in 2013 (pers. comm., DOST-FNRI 2020); and [3] an assumed average weight of 55.0 kg for Asian adults (WHO 2020). However, it is important to note that the daily pork consumption level of the adult Filipino consuming population was assumed as the consumption level for both pork kidneys and pork meat due to the lack of disaggregated data on pork consumption.

Major contributing foods. The NVDRMP of NMIS tested several commodities in the initial monitoring of tissue samples for β-agonists in 2015 and these included beef, chicken, crocodile, and pork. According to CAC/GL 71-2009, the competent authority usually selects the edible tissue as the target to be tested for veterinary drug residues in a residue control program in which marker residues are assumed to occur at the highest concentrations and are most persistent, depending on the primary route of elimination. The NVDRMP of NMIS, in this case, decided to focus their testing and monitoring for 2016–2019 on pork kidneys only, based on their initial screening results. The results, as summarized in Table 11, show that β-agonists were only found present in chicken breast, pork muscle, and mostly in pork kidneys.

Estimate of risk to Beta-agonists in the consumption of pork in the Philippines. Since the consumption of pork in the Philippines is high and there are recorded levels of β-agonist residues in pork, there is a need to ascertain the safety of the consumption of pork by the Filipino consuming population.

As shown in Table 12, the estimated dietary exposures of the Filipino adult consuming population to β-agonist residues in pork meat and pork kidney are significantly

Table 10. Estimated dietary exposures of the Filipino adult consuming population to β-agonist residues in pork.

Commodity	β-agonist residue level [a]		Consumption [b]	Bodyweight [c]	Dietary exposure
	(μg/kg)		(g/day)	(kg)	(μg/kg bw)
Meat	Mean [d]	1.55	396.2	55	0.0111
	Maximum	20.52	396.2	55	0.1478
Kidney	Mean [d]	2.30	396.2	55	0.0166
	Maximum	67.28	396.2	55	0.4847

[a]Assay used for determination was standardized to clenbuterol, therefore it was assumed that the β-agonist residues detected were only clenbuterol (not including ractopamine hydrochloride or zilpaterol hydrochloride)
[b]97.5th percentile daily pork consumption value of the adult Filipino consuming population (pers. comm., DOST-FNRI 2020)
[c]Average weight of Asian adults (EHC 240; WHO 2009)
[d]Lower-bound mean concentration is used for chemicals unlikely to be present unless specifically added in food (EHC 240; WHO 2009)

Table 11. Summary of samples tested for β-agonist residues by NVDRMP of NMIS from 2016–2019.

Commodity	Part	No. of samples	No. of positive samples	No. of Non-detected (ND)	% ND
Beef	Meat	2	0	2	100.0
	Fat	4	0	4	100.0
Chicken	Breast	5	2	3	60.00
	Leg quarter	71	0	71	100.0
	Liver	1	0	1	100.0
	Thigh leg	1	0	1	100.0
Crocodile	Tail muscle	3	0	3	100.0
Pork	Muscle	35	9	26	74.29
	Kidney	1933	636	1297	67.10

"ND" – non-detected

Table 12. Estimated dietary exposures of the adult Filipino consuming population compared to the ADI of clenbuterol.

Commodity		Dietary exposure (μg/kg bw)	ADI of clenbuterol (μg/kg bw)	% ADI
Meat	Mean	0.0111	0–0.004	277.5
	Maximum	0.1478	0–0.004	3,695
Kidney	Mean	0.0166	0–0.004	415
	Maximum	0.4847	0–0.004	12,117.5

higher compared to the ADI of clenbuterol, with values exceeding 100% of the ADI. These results indicate that there is an appreciable risk to the health of the Filipino adult consuming population when it comes to β-agonists in pork.

It is important to note that the exposures were compared to clenbuterol since that was the standard used in the assay and that these calculations do not account for the exposure of Filipinos to ractopamine hydrochloride (ADI = 0–1 μg/kg bw) and zilpaterol hydrochloride (ADI = 0–0.04 μg/kg bw) in pork since this was not included in the monitoring done by NMIS.

Adverse effect levels applied to Philippine exposures. Once the ADI is exceeded, various adverse effects due to acute poisoning such as rapid heartbeat, increase in blood pressure, anxiety, palpitation, and skeletal muscle tremors may be experienced by humans, especially by the vulnerable population (Cheng *et al.* 2016; Lee *et al.* 2017; Luk 2018). However, it must be noted that there were assumptions made in the estimation of risk due to certain gaps identified in the collection of related literature and terms of control measures employed locally. Therefore, the priority should be to fill up the data gaps first to reduce

the uncertainties to produce a more comprehensive risk characterization.

Uncertainties or gaps identified. Upon collection of related literature these were the gaps identified:

1. lack of available dose-response studies focusing on adverse health effects of β-agonists (except for zilpaterol hydrochloride), most studies focus on the therapeutic or bronchodilator effects;
2. no reports or proof of poisoning or illness due to exposure to β-agonists in the Philippines;
3. no available dietary exposure assessment studies on β-agonists in pork in the Philippines and overseas; and
4. lack of disaggregated data on the consumption of pork for a more detailed assessment, specifically by vulnerable groups.

In terms of control measures employed locally:

1. the data on β-agonist residue levels acquired from the results of the NVDRMP of the NMIS focused on pork kidneys and not on the most consumed edible tissue which is the pork meat or muscle,
2. the method used by the NVDRMP of NMIS for the detection and monitoring of β-agonists in pork is standardized to clenbuterol and does not include separate detection of zilpaterol hydrochloride, and
3. the assay done was intended for screening of samples only and positive results were not subjected to a confirmatory test.

Variabilities

1. The β-agonist residue levels in pork vary based on the feeding and withdrawal practices of farmers,
2. The β-agonist residue levels in pork also vary between different tissue samples, and
3. Dose-response and health effects may vary depending on the type of β-agonist present.

Assumptions

These limitations, uncertainties, and variabilities were considered in formulating the following assumptions used in the conduct of the risk profiling:

1. since there was no confirmation on the identity of the β-agonists present and since clenbuterol was used as the standard in the assay, it was assumed that the β-agonist residues detected were clenbuterol;
2. for dietary exposure assessment, the daily pork consumption level of the adult Filipino consuming population was assumed as the consumption level for both pork kidneys and pork meat due to the lack of disaggregated data on pork consumption; and
3. the 97.5th percentile consumption data of the Filipino consuming population was used to provide the most conservative estimate in the computation of the dietary exposure (WHO 2020).

Phase 4: Determination of Available Risk Management Options for β-agonists in Pork

Existing control measures in the Philippines: regulatory and advisory. Table 13 presents the various existing hazard control measures in the Philippines regarding the use of veterinary drugs and feed additives in the production of food-producing animals in the country.

Control measures employed overseas. The general application of veterinary medicinal products within the European Community is administered by the legislative framework of the EU member-states, a series of regulations that set the safety, quality, efficacy, and residue data requirements of these products (Kuiper *et al.* 1998). Table 14 summarizes the various regulations under the EU legislative framework.

Kuiper and co-authors (1998) specifically reported on the illegal use of β-agonists in the European Community. Since β-agonists are only approved for certain veterinary therapeutic uses in the EU (*i.e.* clenbuterol for bronchodilation in horses and calves, and tocolysis in cows), β-agonists are prohibited to be used as growth promoters in farm animals. The extensive use of β-agonists as growth promoters may have reportedly resulted in severe human food poisoning cases. Under Directive 86/469/EEC, the level and frequency of sampling are assigned depending on the contaminant, the species of the animal, and if positive samples have been identified. These surveillance and sampling activities resulted in significantly lower use of clenbuterol in The Netherlands, Germany, Northern Ireland, and the Spanish Basque Country.

The Australian government's Department of Agriculture, Water, and the Environment (DAWE 2020) conducts the Animal Product Residue Monitoring Program under the National Residue Survey, mainly to ensure that Australian products satisfy exporting and importing regulatory requirements. Focusing on veterinary medicines, the chemicals tested usually depend on the likelihood of residue present on the meat samples comprising mainly cattle, sheep, and pigs. The commonly screened chemicals used in the Australian agricultural and veterinary practice include anthelmintics, antibiotics, hormones, and other veterinary drugs such as sedatives, corticosteroids, and β-agonists. According to the random monitoring program

Table 13. Control measures available in the Philippines regarding the use of β-agonist in the production of food-producing animals.

Title	Enforcing official/agency	Control measures
Republic Act No. 1556 An Act to Regulate and Control the Manufacture, Importation, Labelling, Advertising and Sale of Livestock and Poultry Feeds, otherwise known as the "Livestock and Poultry Feeds Act"[a]	Secretary of Agriculture and Natural Resources through the Director, Bureau of Animal Industry	Section 4: Registration d. "No feeds or feeding stuffs in the form of complete mixture, concentrate, supplement or ingredient which have not been registered with the Director, shall be manufactured, imported, advertised, sold or offered for sale or held in possession for sale in the Philippines." Section 7 "An inspector shall be permitted at all reasonable times to enter any premises in which feeds are sold or held in possession for sale or when he has reasonable cause to believe any feed or feeding stuff is being prepared or has been prepared for sale, and may take for analysis samples of any feed or feeding stuff there found without cost." Section 10: Offense and Penalties b. "Any person, partnership, corporation or association which will unlawfully use a registration number, fraudulently lessen or adulterate the feeding value of any feed or feeding stuff, or tamper with packaged feeds for fraudulent purposes, willfully remove, alter, or efface the prescribed tags, labels, markings, or other information placed on packages of feeds or feeding stuffs, fraudulently alter or use certificates of analysis of any official analyst; willfully obstruct, hinder, resist or in any other way oppose an inspector in the execution of his duties under this Act; make unauthorized disposition of feeds placed under detention; import, manufacture, distribute, advertise, sell, or offer for sale or possess for sale by any feed which does not conform with or contravenes the provisions of this Act; or otherwise violate any provision of this Act and the rules and regulations issued thereunder, shall be punished by a fine of not less than one thousand pesos and not more than five thousand pesos or by imprisonment of not more than one year and one day, or by both, in the discretion of the court."
Administrative Order No. 14, Series of 2003, with the Subject: Ban on the Use in Food Animals of Beta-agonist Drugs Used in Human as Bronchodilators and Tocolytic Agents[b]	DA	The Secretary of Agriculture banned the use of human beta-agonist drugs in food animals and prescribe the following: 1. "Application for registration of the same shall be disapproved and immediate revocation of registration, if any, of the above-stated commodity; 2. Stoppage and confiscation of all shipments intended for use in food animals into the country of the above stated commodity at all sea/airports." This ban included beta-agonists such as, but not limited to clenbuterol, salbutamol, terbutaline, and pirbuterol are used as bronchodilators and tocolytic agents in humans. It was also stated that "these beta-agonist drugs are also in food animals as partitioning agents promoting reduction in body fat and enhancing growth." The rationale for banning was due to the fact that "the safety profile of these compounds has not been established and these compounds have been banned in other countries for use as lean-enhancing agent in food animals."
Administrative Order No. 24, Series of 2009, with the Subject: Implementing Guidelines on the National Veterinary Drug Residues Control Program in Foods Pursuant to Administrative Order No. 14, Series of 2006[c]	DA	Section 4: Regulatory Framework 4.1.2 "The BAI, BFAR and FDA shall require the licensing of establishments and registration of veterinary drugs prior to manufacture, importation, distribution, sale, and use." 4.2.1.1 "Food Producing Animal Raisers shall: Ensure that only registered veterinary drugs and products are used in food production in accordance with the conditions imposed by competent authorities including the observance of proper withdrawal period." 4.2.3.2 - 4.2.3.3 "Feed Manufacturers (Commercial and Non-commercial) shall prohibit the incorporation and use of banned veterinary drugs and maintain and update information on the list of banned veterinary drugs." 4.3.2 "The BAI shall ensure that appropriate practices are applied and that effective measures are in place in the proper distribution and use of veterinary drugs in food producing animals production through the conduct of control, verification, reporting and certification in production-related facilities such as but not limited to veterinary drug manufacturing plants, distributors and outlets, warehouses/storages, feed mills, feed stores/outlets, and commercial and backyard farms."

Table 13. Cont.

Administrative Order No. 24, Series of 2009, with the Subject: Implementing Guidelines on the National Veterinary Drug Residues Control Program in Foods Pursuant to Administrative Order No. 14, Series of 2006[c]	DA	4.3.4 "The NMIS shall ensure that control, verification, reporting and certification programs are conducted in post-production establishments such as but not limited to slaughterhouses, poultry dressing plants, meat processing plants, cold storages and meat cutting plants." Section 5: Residue Verification Program 5.1.1 "A verification program shall be implemented to ensure compliance at various control points or point of production thus providing appropriate degree of confidence that practices and controls are adequate for public health safety." 5.3.1 "The BAI, BFAR, NDA, PCC, and NMIS in consultation with FDA shall jointly conduct a risk profiling program to determine the drug residues to be monitored, the frequency and intensity of verification or inspection/audit." Section 6: Sampling 6.1.2 "The BAI shall collect feed samples in feed mills, feed outlets and livestock and poultry farms and collect egg and urine samples from farms for laboratory testing" 6.1.5 "The NMIS shall collect urine, meat samples and other edible tissues in meat establishments, meat shops and other retail outlets." 6.1.7 "The FDA shall conduct verification tests of non-compliant samples within its jurisdiction tested by the DA collecting authorities." Section 8: Regulatory Action 8.1.2 "Establishments responsible for the products with residues exceeding the allowable limit shall be investigated by competent authorities in determining the root cause of the non-compliance/non-conformance, records of distribution to different outlets and risk management, and its impact on health and public safety." 8.2.1 "Proportionate action shall be taken when non-compliance is the result of either negligence or intentional act." 8.3.1 "Non-compliant animal food products shall not be passed for human consumption and shall be disposed of accordingly." Section 10: Penalties and Sanctions "After due notice and hearing, the competent authorities shall impose the proper sanctions and penalties and conduct appropriate corrective actions on concerned persons, products, and establishments."
Republic Act 10611 "An Act to Strengthen the Food Safety Regulatory System in the Country to Protect Consumer Health and Facilitate Market Access of Local Foods and Food Products, and for Other Purposes," otherwise known as the "Food Safety Act of 2013"[d]	DA Department of Health	Section 3: Objectives "Protect the public from food-borne and water-borne illnesses and unsanitary, unwholesome, misbranded or adulterated foods." Section 7: Use of Science-based Risk Analysis "The risk analysis shall cover all hazards directly or indirectly, intentionally or unintentionally introduced into the food. This shall include hazards coming from packaging materials, cleaning agents, and other sources." Section 8: Protection of Consumer Interests "The protection of consumer interest shall be geared towards the prevention of adulteration, misbranding, fraudulent practices and other practices which mislead the consumer." Section 13: Principal Responsibility of Food Business Operators 13.2 "FBOs shall ensure that foods they produce are prepared according to standards, codes of practice and other control measures as prescribed by the FSRAs that prevent or minimize food safety hazards or reduce the hazards to acceptable levels." Section 14: Specific Responsibilities of Food Business Operators 14a. "The FBOs shall ensure that such food is not adulterated, contaminated, misbranded, and misleading. FBOs shall monitor the performance of control measures and maintain monitoring records as a matter of routine practice."

Table 13. Cont.

Republic Act 10611 "An Act to Strengthen the Food Safety Regulatory System in the Country to Protect Consumer Health and Facilitate Market Access of Local Foods and Food Products, and for Other Purposes," otherwise known as the "Food Safety Act of 2013"[d]	DA Department of Health	Section 34: Food-borne Illness Monitoring and Surveillance 34b.1 "The DA and DOH shall link and coordinate their activities in identifying and monitoring hazards in the food supply chain such as pesticide residues, food additives, veterinary drug residues in food and chemical, biological, and other contaminants under their jurisdiction. The results shall be used to create a database on the national food safety situation."
NVDRMP, created by virtue of DA-AO No. 14 s. 2006 [e]	DA-NMIS	NMIS was tasked to analyze samples of meat, urine, and edible tissues for the presence of regulated veterinary drugs and any banned veterinary drugs including β-agonist, chloramphenicol, nitrofuran, and corticosteroids. The monitoring of banned veterinary drugs is done biannually and through a quantitative screening test utilizing the Elisa method.

[a]BAI (1956)
[b]BAI (2003)
[c]NMIS (2009)
[d]Official Gazette (2015)
[e]NMIS (2006)

Table 14. Regulations of the European Union Legislative Framework (EC n/d).

Regulation	Function
Regulation (EU) No 37/2010	Establishes maximum residue limits (MRLs) of veterinary medicinal products in food-producing animals and animal products
Commission Regulation (EC) 1881/2006	Lays down maximum limits (MLs) for the presence of certain contaminants in animal products
Council Directive 96/23/EC	Lays down measures to monitor certain substances and residues thereof, mainly veterinary medicinal products, in live animals and animal products
Commission Decision 97/747/EC	Lays down levels and frequencies of sampling for certain animal products

results for 2017–2018, the compliance rates of the meat programs ranged from 96–100%.

The Agricultural Marketing Service (AMS-USDA n/d) of the United States Department of Agriculture, under the Livestock and Poultry Program monitoring and verification, authorizes the Never Fed Beta Agonists marketing claim available for companies that produce livestock, beef, and pork products. This claim will state to customers that the meat is derived from animals that were never fed β-agonists and is free of β-agonist residues. A customer program will only be approved once it has been audited and approved by the AMS that its products are produced under an approved quality management system and are in conformance with the Never Fed Beta Agonist Program requirements.

In Canada, the Canadian Food Inspection Agency (CFIA) heads the Canadian Beta Agonist-Free Beef Certification Program, for cattle and beef industries, which aims to conform to import requirements by countries that do not allow the use of feeds added with β-agonists during animal production for meat intended for human consumption. Conformity with the requirements depends on the individual responsibility of operators. Certification tests include abattoir monitoring by CFIA and feedlot testing through a third-party auditor (Government of Canada 2017).

Control options. The following are the recommendations aimed at improving the control of the use of β-agonists in pork production:

- the definition of β-agonists in Administrative Order No. 14, s. 2003 of the DA should specifically state all β-agonists used as bronchodilators and tocolytic agents in humans which are included in the ban;
- conduct intensive educational campaigns and/or awareness seminars to emphasize to the LGUs and stakeholders that the use of human β-agonist drugs in food animals is not allowed;
- the import of β-agonists intended for human use in the country should be traced and monitored through the joint efforts of the BOC, FDA, and BAI from the point of entry up to the end-user to make sure that these are not just imported to be intentionally used as feed additives;

- capacitate LGUs and regional offices to monitor products sold in Agrivet supply stores and ingredients used in feed mills;
- capacitate NMIS to conduct confirmatory testing on β-agonist positive samples to determine the identity of the drug residue;
- regarding the use of allowed β-agonists in pork production such as ractopamine, the practice of withdrawal period should be implemented by the stakeholders and strictly monitored by LGUs; and
- moreover, the presence of β-agonists in other edible tissues is also possible and may increase the level of intake of any banned growth-promoting substances; a total diet study is recommended to have a better picture of the risk of consuming meat products that may contain β-agonists.

CONCLUSION

This risk profile brings together information on the risks that may be associated with β-agonists in the consumption of pork in the Philippines, which is to provide an objective analysis of scientific data and information on β-agonists in pork so that risk managers (*i.e.* NMIS, BAFS, BAI) can make decisions and, if necessary, take further action.

Despite the gaps identified, the risk was estimated for the mean and maximum dietary exposures of the Filipino adult consuming population to β-agonists in pork meat (0.0111 and 0.1478 μg/kg bw) and pork kidney (0.0166 and 0.4847 μg/kg bw) are significantly higher compared to the ADI of clenbuterol (0–0.004 μg/kg bw), with values exceeding 100% of the ADI. These results indicate that there is an appreciable risk to the health of the general Filipino population when it comes to β-agonists in pork.

ACKNOWLEDGMENTS

The project team wishes to acknowledge the following agencies:

- the DOST as the funding agency;
- the University of the Philippines Diliman (UPD), College of Home Economics, Department of Food Science and Nutrition as the implementing agency;
- the DOST–Philippine Council for Industry, Energy and Emerging Technology Research and Development) as the funding monitoring agency; and
- the UPD–Office of the Vice Chancellor for Research and Development–Research Management Office as the implementing monitoring agency.

The project team would also like to thank the following collaborating offices:

- the DA-NMIS for access to monitoring data,
- the DOST-FNRI for access to food consumption data, and
- Philippine local government units for assistance in the communication with local veterinarians.

NOTES ON APPENDICES

The complete appendices section of the study is accessible at https://philjournsci.dost.gov.ph

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