EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 May 2024
EMA/CVMP/189263/2024
Veterinary Medicines Division

European public MRL assessment report (EPMAR)

Sodium salicylate (poultry other than turkey)

On 18 March 2024 the European Commission adopted a Regulation[1] establishing maximum residue limits for sodium salicylate in poultry other than turkey, valid throughout the European Union. These maximum residue limits were based on the favourable opinion and the assessment report adopted by the Committee for Veterinary Medicinal Products.

Sodium salicylate is intended for use in poultry other than turkey for the symptomatic treatment of febrile conditions and mild to moderate pain at a dose of 40 mg/kg bodyweight (bw)/day for a maximum of 3 consecutive days administered via drinking water.

Sodium salicylate had maximum residue limits already established for bovine and porcine (no MRL required classification, for oral use) as well as all food-producing species except fin fish (no MRL required classification, for topical use)[2] and turkey (numerical MRLs)[3].

Dopharma B.V. submitted to the European Medicines Agency an application for the extension of maximum residue limits on 30 September 2022.

Based on the original and complementary data in the dossier, the Committee for Veterinary Medicinal Products recommended on 5 October 2023 the extension of maximum residue limits for sodium salicylate to poultry other than turkey.

Subsequently, the Commission recommended that maximum residue limits in chicken and poultry other than turkey are established. This recommendation was confirmed on 22 February 2024 by the Standing Committee on Veterinary Medicinal Products and adopted by the European Commission on 18 March 2024.

[1] Commission Implementing Regulation (EU) No 2024/859, OJ L, 2024/859 of 19.3.2024
[2] Commission Regulation (EU) No 37/2010, OJ L 15 of 20.1.2010
[3] Commission Implementing Regulation (EU) No 1191/2012, OJ L 340 of 13.12.2012

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Summary of the scientific discussion for the establishment of MRLs

Substance name:	Sodium salicylate
Therapeutic class:	Anti-inflammatory agents/Non-steroidal anti-inflammatory agents
Procedure number:	EMEA/V/MRL/003420/EXTN/0004
Applicant:	Dopharma B.V.
Target species applied for:	Chicken
Intended therapeutic indication:	Symptomatic treatment of febrile conditions and mild to moderate pain
Route(s) of administration:	Oral

1. Introduction

Sodium salicylate is the sodium salt of salicylic acid and is used in human and veterinary medicinal products intended for topical or oral administration due to its keratinolytic as well as antipyretic, antiphlogistic and analgesic properties.

In the context of the present extension application, sodium salicylate is intended for oral use in chickens for the symptomatic treatment of febrile conditions and mild to moderate pain at a dose of 40 mg/kg bodyweight (bw)/day for a maximum of 3 consecutive days administered via drinking water.

Sodium salicylate was previously assessed by the CVMP and a pharmacological ADI of 7.3 µg/kg bw, i.e. 440 µg/person, was established.

Currently, sodium salicylate is included in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 in accordance with the following table:

Pharmaco-logically active substance	**Marker residue**	**Animal species**	**MRLs**	**Target tissues**	**Other provisions**	**Therapeutic classification**
Sodium salicylate	NOT APPLICABLE	Bovine, porcine	No MRL required	NOT APPLICABLE	For oral use. Not for use in animals from which milk is produced for human consumption.	NO ENTRY
		All food producing species except fin fish	No MRL required	NOT APPLICABLE	For topical use only.	
	Salicylic acid	Turkey	400 µg/kg 2,500 µg/kg 200 µg/kg 150 µg/kg	Muscle Skin and fat in natural proportions Liver Kidney	Not for use in animals producing eggs for human consumption.	Anti-inflammatory agents/Non-steroidal anti-inflammatory agents

2. Scientific risk assessment

2.1. Safety assessment

The CVMP has previously assessed the consumer safety of sodium salicylate and established a pharmacological ADI of 7.3 µg/kg bw, i.e. 440 µg/person, based on the ADI (8.3 µg/kg bw or 500 µg/person) established for acetylsalicylic acid adjusted to appropriate sodium salicylate equivalents. Salicylic acid is the active component in both substances and both of the above ADIs equate to a salicylic acid ADI of 6.3 µg/kg bw or 380 µg/person). As no change to the established ADI is proposed, no further assessment regarding the consumer safety of the substance is required for the purpose of this extension application.

2.2. Residues assessment

2.2.1. Pharmacokinetics in target species

Pharmacokinetics and bioavailability of salicylic acid in chickens was investigated in a non-GLP-compliant pilot study. The experiment was conducted in a one-period crossover design including 2 groups of 6 clinically healthy broilers (mean bw: 2.39 ± 0.14 kg). For the intravenous reference administration, a solution containing 50 mg sodium salicylate per ml was administered through an intravenous (i.v.) cannula at a dose of 50 mg/kg bw. For the oral administration, sodium salicylate was dissolved in a limited amount of drinking water and administered orally using a crop tube at a dose of 100 mg sodium salicylate per kg bw.

Blood samples were drawn before and approximately 5, 30, 60 and 90 minutes as well as 2, 3, 4, 6, 9, 12, 16 and 24 hours after administration.

Salicylic acid was rapidly absorbed following oral administration with a mean absorption half-life of 1.27 hours. The time to reach the highest plasma concentration (T_{max}) was 3.2 hours and the elimination half-life was 3.5 hours. Bioavailability was calculated to be 108%.

In another GLP-compliant study, the pharmacokinetics of acetylsalicylic acid and sodium salicylate in chickens were compared. This experiment was conducted in a two-period parallel design including 32 clinically healthy broilers (mean bw: 3.38 ± 0.51 kg). For both phases, the animals were divided into four experimental groups of four animals each. The time between the two phases was seven days. Acetylsalicylic acid was suspended in a limited amount of drinking water and administered orally using a crop tube at a dose of 50 mg per kg bw. Sodium salicylate was dissolved in a limited amount of drinking water and administered orally using a crop tube at a dose of 40, 45 and 50 mg/kg bw. Blood samples were drawn via an i.v. cannula before and approximately 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, 24, 32 and 48 hours after administration. Plasma concentration-time curves of salicylic acid were evaluated by means of non-compartmental analysis. Due to technical issues, results from animals receiving acetylsalicylic acid in phase 1 were excluded from the statistical analysis.

The peak plasma concentrations (C_{max}) in groups receiving 50 mg/kg bw acetylsalicylic acid as well as 40, 45 and 50 mg/kg bw sodium salicylate were 58.4 ± 9.8, 72 ± 8, 75 ± 5 and 82 ± 8 µg/ml, respectively. T_{max} in the groups receiving 50 mg/kg bw acetylsalicylic acid as well as 40, 45 and 50 mg/kg bw sodium salicylate was 2.37 ± 0.62, 1.4 ± 0.9, 1.2 ± 0.6 and 1.5 ± 0.9 hours, respectively, while AUC was 648 ± 222, 820 ± 176, 811 ± 141 and 998 ± 123 h*µg/ml, respectively. The elimination half-life was 3.33 ± 1.21, 3.4 ± 1.2, 3.5 ±0.9 and 4.3 ± 0.9 h for groups receiving 50 mg/kg bw acetylsalicylic acid as well as 40, 45 and 50 mg/kg bw sodium salicylate, respectively.

An ANOVA analysis of the data from the 2nd experimental phase with the reference product (acetylsalicylic acid) and the equimolar test group (44.4 mg/kg sodium salicylate) showed no statistically significant differences regarding the AUC, with the ratio test/reference being 1.3. For C_{max}, a similar ratio of test/reference was calculated (1.3), albeit a statistically significant difference ($p = 0.004$) was observed. Likewise, T_{max} was significantly longer following the administration of the reference product (acetylsalicylic acid) when compared to the test product (sodium salicylate).

2.2.2. Residue depletion studies

Depletion in tissues

A pilot non-GLP-compliant study was performed to determine the residue depletion of salicylic acid after the repeated oral administration of sodium salicylate in 18 (4 males, 14 females) clinically healthy 7-week old Hubbard chickens. Twelve animals received the test item, while 6 animals were not medicated and were used as baseline controls for the determination of salicylate residues originating from feed as it contained approximately 0.6 mg of salicylic acid per kg. Sodium salicylate (NA-SALICYLAAT, 100%, Powder for solution for oral administration) was administered orally through the drinking water at a target dose of 50 mg/kg bw once or twice daily during 6 consecutive days as follows: BID (100 mg/kg bw/day) on day 1, 2, 4 and 5 and SID (50 mg/kg bw/day) on days 3 and 6. Plasma samples were taken 3 and 6 hours after the administration and at time of slaughter. The animals were slaughtered at 12 and 36 hours after cessation of the medication. Control animals were slaughtered at 12 hours. Salicylic acid plasma and tissue samples were analysed using validated methods of analysis (UPLC), with the LOQ for plasma and tissues being 0.5 µg/ml and 52.56 µg/kg, respectively. In control animals, all plasma and tissue samples were below the LOQ of the analytical method at all times, indicating that the feed was not the source of salicylic acid residues. In treated animals, plasma salicylic acid concentrations ranged from 11.6–54.0 µg/ml at 3 hours and from 26.4–66.3 µg/ml at 6 hours. All plasma samples were below the LOQ at 12 and 36 hours after the last administration. Residues above the LOQ were found in liver, kidney and skin/fat. The highest value (156 µg/kg) was found in the kidney at 12 hours. Residues in muscle were below the LOQ in animals at all times.

A GLP-compliant study was conducted to determine the depletion of salicylic acid following the recommended sodium salicylate treatment in 28 (15 males, 13 females) 8-week-old clinically healthy Hubbard chickens (mean bw: 2.5 ± 0.3 kg at the start of the clinical phase). 24 animals received the test item and 4 animals were not medicated in order to determine baseline control salicylate residue levels originating from feed. The animals were housed in individual cages. Sodium salicylate (NA-SALICYLAAT, 100%, Powder for solution for oral Administration) was administered orally through the drinking water at a target dose of 40 mg/kg bw during 3 consecutive days. Plasma samples were taken 3 and 6 hours after administration of the treatment and at time of slaughter. Medicated animals were slaughtered in groups of six at approximately 12, 24, 48 and 72 hours after cessation of the medication. The control animals were slaughtered at 12 hours after cessation of the placebo treatment. Plasma and tissue samples were analysed using validated methods of analysis (UPLC-MS-MS), with the LOQ in plasma and tissue samples being 0.5 and 52.56 µg/kg, respectively. Plasma and tissue concentrations in the control animals were all below the LOQ of the analytical method, indicating that the feed was not the source of salicylic acid residues. In treated animals, plasma salicylic acid concentrations ranged from 10.5–30.4 µg/ml at 3 hours and from 14.5–33.8 µg/ml at 6 hours post treatment. All plasma samples were below the LOQ at slaughter. In kidney, liver, fat/skin and muscle samples, salicylic acid residue concentrations were very low. At 12 hours after cessation of the medication, residues were only found in all kidney samples (144–283 µg/kg), albeit residue

concentrations above the LOQ in muscle and liver of one animal were observed. At 24 hours, residues above the LOQ in the kidney of one animal were found, while residue levels were below the LOQ in all tissues at 48 hours. Interestingly, at 72 hours, residues just above the LOQ were detected in the kidney of one animal. In skin/fat samples, residue concentrations were below LOQ at all time points.

A further GLP-compliant study was conducted to determine the depletion of salicylic acid following the recommended sodium salicylate treatment in 22 (12 males, 10 females) 10-week-old clinically healthy Hubbard chickens (mean bw: 3.22 ± 0.38 kg at the start of the clinical phase). Eighteen animals received the test item, while 4 animals were not medicated and were used as baseline controls for the determination of salicylate residues originating from feed. Sodium salicylate (NA-SALICYLAAT, 100%, Powder for solution for oral Administration) was administered orally through the drinking water at a target dose of 40 mg/kg bw during 3 consecutive days. The animals were housed in individual cages. Plasma samples were taken before administration and at the time of slaughter. Medicated animals were slaughtered in groups of six either approximately 6 hours after the beginning of the first medication, approximately 2 hours after the beginning of the last administration (50 hours) or approximately 3 hours after cessation of the medication. The control animals were slaughtered after the beginning of the last administration. Plasma and tissue samples were analysed using validated methods of analysis (UPLC-MS-MS), with the LOQ in plasma and tissues being 0.5 and 52.56 µg/kg, respectively. Plasma samples taken before administration of the test product as well as from the control animals did not contain measurable concentrations of salicylic acid. Plasma levels at slaughter timepoints during sodium salicylate administration were in the range of 18.1–28.8 µg/ml at 6 hours and 23.6–49.4 µg/ml at 50 hours. At 3 hours after the end of treatment, the plasma concentrations were lower (5.8–17.1 µg/ml). Tissue concentrations of the control animals were all below the LOQ of the analytical method except for one kidney sample, which was probably due to contamination. It was thus assumed that the feed was not a source of relevant salicylic acid residues. During treatment with sodium salicylate, substantial concentrations of salicylic acid were found in all edible tissues. The highest concentrations were found in kidney, followed by liver, muscle and skin/fat. Approximately 6 hours after the beginning of the medication, salicylic acid concentrations varied from 7,552–13,189 ng/g (mean ± SD: 10,824 ± 2,149 ng/g) in kidney, 4,802–8,573 ng/g in liver (mean ± SD: 6,005 ± 1,411 ng/g), 2,062–4,375 ng/g (mean ± SD: 3,133 ± 910 ng/g) in muscle and 371–4,721 ng/g (mean ± SD: 2346 ± 1914 ng/g) in skin/fat. Approximately 50 hours after the beginning of the treatment, salicylic acid concentrations varied from 12,220–19,517 ng/g (mean ± SD: 16305 ± 2499) in kidney, 6,436–10,263 ng/g (mean ± SD: 8,824 ± 1,483) in liver, 3,444–5,711 ng/g (mean ± SD: 4,886 ± 827) in muscle and 702–2,298 ng/g (1,566 ± 533) in skin/fat. Distribution remained highest in the kidney, followed by the liver and muscle, the latter containing about equal amounts to skin/fat. Approximately 3 hours after the cessation of the treatment, concentrations of salicylic acid remained highest in kidney (4531 ± 1720 ng/g), followed by liver (2469 ± 1023 ng/g) and approximately equal concentrations in muscle (1034 ± 430 ng/g) and skin/fat (1231 ± 933 ng/g).

Depletion in milk/eggs

No residue data were provided for eggs.

Selection of marker residue and ratio of marker to total residues

Salicylic acid is generally recognised as the marker residue for salicylates. As salicylic acid is the active metabolite for salicylates, the ratio of marker to total residues is considered to be 1.

2.2.3. Monitoring or exposure data

It is plausible that salicylic acid ingested via plant material in the feed can lead to increased salicylic acid levels in products of animal origin, such as meat and milk.

One study determined that laying hens fed fresh corn, which naturally contains salicylic acid, laid eggs in which salicylic acid was also detected. The same study concluded that exposure of chickens to salicylates at feed additive levels and to naturally occurring salicylates results in low residue concentrations and rapid depletion of salicylic acid (Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2020;37(6):946–954. doi: 10.1080/19440049.2020.1744740).

2.2.4. Analytical method for monitoring of residues

A selective UPLC-MS-MS analytical method for the detection of salicylic acid in edible poultry tissues is available. The method is presented in an internationally recognised format and has been validated in line with the requirements of VICH GL49. The limits of quantification for salicylic acid for muscle, liver, kidney and skin/fat are 34, 26, 75 and 29 µg/kg, respectively. The possible presence of endogenous salicylic acid residues in tissues has been taken into account during the validation of the method.

The described method of analysis utilizes commercially available standards, reagents and equipment.

The relevant European Reference Laboratory (EURL) has reviewed the analytical method and confirmed its suitability.

2.2.5. Potential effects on the microorganisms used for industrial food processing

As the substance is not expected to possess antimicrobial activity, no effects on microorganisms used for industrial food processing are expected.

2.2.6. Findings of EU or international scientific bodies

No MRLs for sodium salicylate have been established by the Codex Alimentarius.

In 2019, the European Commission's Scientific Committee on Consumer Safety (SCCS) published an opinion on cosmetics containing salicylic acid (SCCS/1601/18). Salicylic acid was found to be safe when used as a preservative at a concentration of up to 0.5% in cosmetic products.

The European Chemicals Agency (ECHA) reviewed salicylic acid in relation to its use in Product Type (PT) 2, 3 and 4 biocides. Of most relevance is the use in PT3 products used for disinfection of dairy cow teats pre and post milking. None of the uses are expected to result in significant consumer exposure and, as such, these evaluations are not considered to impact on the outcome of the current evaluation.

3. Risk management recommendations

3.1. Availability of alternative medicines and other legitimate factors

Feasibility of controls

Residue depletion data demonstrate that residues in kidney can be expected to deplete to the relevant MRL more slowly than residues in other tissues. Consequently, the CVMP recommends that, where the entire carcass is available, monitoring of residues of sodium salicylate should focus on kidney samples, as compliance with the kidney MRL can be expected to indicate that residues in other tissues will also be compliant with their respective MRLs.

Salicylate intake through feed ingestion is not expected to interfere with residue control as control animals receiving feed with natural levels of salicylates showed no residue levels above the LOQ in edible tissues. Therefore, interference with residue control methods resulting from endogenous sodium salicylate levels is not expected. However, it is noted that a range of salicylic acid-yielding active substances are approved for use in the same species and that these currently have a "No MRL required" status. Therefore, detection of salicylic acid/salicylate residues will provide no information on whether residues are the result of use of a veterinary medicinal product containing sodium salicylate or a veterinary medicinal product containing an alternative source of salicylic acid/salicylate.

Conditions of use

In the absence of MRLs for eggs, the use of sodium salicylate is restricted to animals not producing eggs for human consumption.

Other factors that should, if applicable, be taken into consideration in support of the MRL recommendation:

A "No MRL required" classification has previously been established for sodium salicylate in cattle and pigs for oral use only and for all food-producing species except fin fish for topical use only. For turkeys, numerical MRLs have been established for muscle, skin/fat, liver and kidney without restriction to the route of administration. Moreover, the circumstances under which many broilers are bred today makes it possible to execute slaughter within three hours after the last dosing. Based on data from the final residue depletion study at this time point residues will amount to approximately 188% of the ADI and hence, consumer safety cannot be ensured.

Furthermore, in order to meet the requirements for a "No MRL required" classification, Regulation (EU) 2018/782 states that consumer exposure to residues should always (i.e. at every timepoint on the residue depletion curve) remain at safe levels, i.e. below the ADI or alternative limit. As the total residue intake would be equivalent to 188% of the ADI 3 hours post treatment, this requirement is clearly not fulfilled in the present case. In addition, these calculations were performed by using mean concentration values only, instead of using 95/95% tolerance limits for the residue data of each individual tissue.

The data demonstrate that residue depletion in chickens is rapid and also that tissue distribution in chickens differs from that seen in turkeys. At 3 hours after the end of treatment, the consumer exposure represents 1684% of the ADI based on the 95%/95% upper tolerance limits. At 12 hours, and based on the 95%/95% upper tolerance limit in kidney tissue and the highest residues values in

other tissues (muscle tissue of one animal contained 1226 µg/kg residues well above the suggested MRL), the consumer exposure represents 101% of the ADI.

In light of the above as well as the fact that chickens are a major species, and for consistency with the approach taken for turkeys, it would be advisable to set numerical MRLs.

3.2. Elaboration of MRLs

Based on the distribution pattern of salicylic acid seen in chickens, the recommended MRL values are shown in the table below, which would lead to consumer intake of residues as indicated therein.

Edible tissue or products (poultry)	**Daily consumption (kg)**	**MRL proposal (µg/kg)**	**Ratio of the marker/total residue**	**Amount per edible tissue or product**
Muscle	0.30	250	1	75
Skin/Fat	0.09	250	1	22.5
Liver	0.10	500	1	50
Kidney	0.01	1000	1	10
Total estimated daily intake (µg/person)				**157.5**

These MRLs reflect the relative distribution seen in the depletion study at 3 hours after the end of treatment, and would result in a total intake of salicylic acid equivalent to 41% of the ADI of 380 µg per person[4]. Additional consumer intake at the level of the milk MRL of 9 µg/kg for salicylic acid, established for aluminium salicylate, would increase the estimated total daily intake to 171 µg (45% of the ADI).

[4] Since salicylic acid was the measured residue, the ADI used in this calculation is the ADI for salicylic acid rather than the ADI for sodium salicylate.

4. Considerations on possible extrapolation of MRLs

In line with Article 5 of Regulation (EC) No 470/2009, the CVMP considered the possibility of extrapolating the maximum residue established for sodium salicylate on the basis of residue data in chicken to other food-producing species and commodities. Taking into account the provisions laid down in Regulation (EU) 2017/880, the recommendations on extrapolation are justified as follows:

Animal species/ food commodities	**Extrapolation possible (Yes/No)**	**Justification**
Poultry species other than turkeys	Yes	Extrapolation to poultry is possible, as the marker residue salicylic acid has been detected in several bird species following intravenous sodium salicylate administration. Extrapolation to turkey is not recommended, as different numerical values are already established.

5. Conclusions and recommendation for the establishment of maximum residue limits

Having considered that:

- a pharmacological ADI of 0.0083 mg/kg bw, i.e. 0.5 mg/person, established for acetylsalicylic acid is considered relevant for sodium salicylate. However, in order to take account of the difference in molecular weights and taking account of the fact that residues are measured as salicylic acid, the ADI was recalculated to be equivalent to 0.38 mg/person salicylic acid;
- salicylic acid was retained as the marker residue;
- the marker to total residues ratio is considered to be 1, as the marker residue, salicylic acid, is considered to be the only pharmacologically active residue;
- a validated analytical method for the detection of residues in chicken tissues is available indicating that residues in edible tissues can be adequately monitored;
- extrapolation to poultry, except turkey, is appropriate,

the Committee recommends the extension of maximum residue limits for sodium salicylate. Furthermore, with reference to Article 5 of Regulation (EC) No 470/2009, and in line with the criteria laid down in Regulation (EU) 2017/880, the Committee recommends the extrapolation of the maximum residue limits to poultry species other than turkey. Therefore, the Committee recommends, by consensus, the amendment of the entry for sodium salicylate in Table 1 of the Annex to Commission Regulation (EU) No 37/2010 as follows:

Pharmaco-logically active substance	Marker residue	Animal species	MRLs	Target tissues	Other provisions	Therapeutic classification
Sodium salicylate	NOT APPLICABLE	Bovine, porcine	No MRL required	NOT APPLICABLE	For oral use. Not for use in animals from which milk is produced for human consumption.	NO ENTRY
		All food producing species except fin fish	No MRL required		For topical use only.	
	salicylic acid	Turkey	400 µg/kg	Muscle	Not for use in animals producing eggs for human consumption.	Anti-inflammatory agents/Non-steroidal anti-inflammatory agents
			2,500 µg/kg	Skin and fat in natural proportions		
			200 µg/kg	Liver		
			150 µg/kg	Kidney		
		Poultry other than turkey	250 µg/kg	Muscle		
			250 µg/kg	Skin and fat in natural proportions		
			500 µg/kg	Liver		
			1000 µg/kg	Kidney		

Taking into account the MRL established for aluminium salicylate in bovine milk, the theoretical maximum daily intake of residues from chicken tissues and bovine milk represents 45% of the ADI for salicylic acid.

6. Background information to the procedure

Submission of the dossier:	30 September 2022
Steps taken for assessment of the substance	
Application validated:	19 October 2022
Clock started:	20 October 2022
List of questions adopted:	5 February 2023
Consolidated response to list of questions submitted:	4 July 2023
Clock re-started:	10 July 2023
CVMP opinion adopted:	5 October 2023