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Assessment of the application for renewal of authorisation of zinc chelate of hydroxy analogue of methionine for all animal species

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Abstract

The Panel on Additives and Products or Substances used in Animal Feed (FEEDAP) was asked to deliver a scientific opinion on the application for renewal of authorisation of zinc chelate of hydroxy analogue of methionine (Mintrex[®]Zn) for all animal species. The FEEDAP Panel has delivered three opinions (during 2008 and 2009) on the safety and efficacy of the additive. The additive was authorised in 2010 as 'Zinc chelate of hydroxy analogue of methionine' containing 17.5–18 % zinc, 81 % (2-hydroxy-4-methylthio)butanoic acid (DL-methionine hydroxy analogue, HMTBa) and maximum 1% mineral oil. Following some modifications in the manufacturing process, the additive does not contain mineral oil and the applicant proposes the following specifications: $\geq 17\%$ zinc and $\geq 79\%$ HMTBa. The data provided indicate that the additive complies with the new specifications. No new evidence was found that would make the FEEDAP Panel reconsidering its previous conclusions on the safety for target species, consumers and environment. The applicant provided new studies on the effects of the additive on the respiratory tract and on skin and eyes. Data on the characterisation of the additive and the new studies on skin/eyes led the Panel to reconsider the safety for the user. Owing to the zinc and nickel content of Mintrex[®]Zn, the handling of the additive poses a risk to users by inhalation; the additive is not a skin or eye irritant but is considered a skin sensitiser. The present application did not include a proposal for amending or supplementing the conditions of the original authorisation that would have an impact on the efficacy of the additive; therefore, there was no need for assessing the efficacy of the additive in the context of the renewal of the authorisation.

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

Regulation (EC) No 1831/2003¹ establishes the rules governing the Community authorisation of additives for use in animal nutrition. In particular, Article 14(1) of that Regulation lays down that an application for renewal shall be sent to the Commission at the latest one year before the expiry date of the authorisation.

The European Commission received a request from Novus Europe S.A./N.V.² for renewal of the authorisation of zinc chelate of hydroxy analogue of methionine, when used as a feed additive for all animal species (category: nutritional additives; functional group: compounds of trace elements).

According to Article 7(1) of Regulation (EC) No 1831/2003, the Commission forwarded the application to the European Food Safety Authority (EFSA) as an application under Article 14(1) (renewal of the authorisation). EFSA received directly from the applicant the technical dossier in support of this application. The particulars and documents in support of the application were considered valid by EFSA as of 9 July 2019.

According to Article 8 of Regulation (EC) No 1831/2003, EFSA, after verifying the particulars and documents submitted by the applicant, shall undertake an assessment in order to determine whether the feed additive complies with the conditions laid down in Article 5. EFSA shall deliver an opinion on the safety for the target animals, consumer, user and the environment and on the efficacy of the product zinc chelate of hydroxy analogue of methionine, when used under the proposed conditions of use (see Section 3.1.4).

1.2. Additional information

The FEEDAP Panel has adopted three opinions on zinc chelate of hydroxy analogue of methionine as feed additive for all species: a first one on the safety and efficacy of the additive (EFSA, 2008), a second one on the safety for target species (EFSA, 2009), and the third one on the safety for the target species and safety for the consumers (EFSA FEEDAP Panel, 2009).

Zinc chelate of hydroxy analogue of methionine is authorised in the European Union since 2010 as a nutritional additive for all animal species (3b6.10).³ The authorisation was amended in 2016, regarding the maximum content of zinc in complete feed.⁴

2. Data and methodologies

2.1. Data

The present assessment is based on data submitted by the applicant in the form of a technical dossier⁵ in support of the authorisation request for the use of zinc chelate of hydroxy analogue of methionine as a feed additive.

The European Union Reference Laboratory (EURL) considered that the conclusions and recommendations reached in the previous assessment are valid and applicable for the current application.⁶

2.2. Methodologies

The approach followed by the FEEDAP Panel to assess the safety and the efficacy of zinc chelate of hydroxy analogue of methionine is in line with the principles laid down in Regulation (EC) No 429/2008⁷

¹ Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 on additives for use in animal nutrition. OJ L 268, 18.10.2003, p. 29.

² Novus Europe S.A./N.V. Woluwe Atrium - 5th Floor, Rue Nerveldstraat 101-103. BE-1200 Brussels.

³ Commission Regulation (EU) No 335/2010 of 22 April 2010 concerning the authorisation of zinc chelate of hydroxy analogue of methionine as a feed additive for all animal species. OJ L 102, 23.4.2010, p. 22.

⁴ Commission Implementing Regulation (EU) 2016/1095 of 6 July 2016 concerning the authorization of zinc compounds. OJ L 182, 7.7.2016, p. 7.

⁵ FEED dossier reference: FAD-2019-0034.

⁶ The report linked to the previous dossier (related to EFSA-Q-2007-098) is available on the EURL website: <https://ec.europa.eu/jrc/sites/jrcsh/files/FinRep-FAD-2007-0010.pdf>

⁷ Commission Regulation (EC) No 429/2008 of 25 April 2008 on detailed rules for the implementation of Regulation (EC) No 1831/2003 of the European Parliament and of the Council as regards the preparation and the presentation of applications and the assessment and the authorisation of feed additives. OJ L 133, 22.5.2008, p. 1.

and the relevant guidance document: Guidance on the renewal of the authorisation of feed additives (EFSA FEEDAP Panel, 2013).

3. Assessment

The additive 'Zinc chelate of hydroxy analogue of methionine' is authorised as nutritional additive (functional group: compounds of trace elements) as a source of zinc for all animal species. The maximum content of zinc authorised in animal feed, established in the Commission Implementing Regulation (EU) 2016/1095, ranges from 120 to 200 mg/kg complete feed depending on the animal species/categories (for more details see section 3.1.4).

This assessment regards the renewal of the authorisation of the additive. From here onwards, the additive will be referred to as 'Mintrex[®]Zn', the trade name of the additive.

3.1. Characterisation

The additive is authorised as 'Zinc chelate of hydroxy analogue of methionine' containing 17.5–18% zinc and 81% (2-hydroxy-4-methylthio)butanoic acid (DL-methionine hydroxy analogue, HMTBa), and maximum 1% mineral oil. The applicant declared that, since the additive was authorised, some modifications have been introduced in the manufacturing process:

[REDACTED]. These modifications have led to a slightly different additive composition, and thus, the applicant proposes the following specifications: $\geq 17\%$ zinc and $\geq 79\%$ HMTBa; this represents a variation compared to the current authorisation.

3.1.1. Characterisation of the additive

The chemical name of the additive is zinc bis(-2-hydroxy-4-methylthio)butanoate. The structural formula is $\text{Zn}(\text{CH}_3\text{S}(\text{CH}_2)_2\text{-CH}(\text{OH})\text{-COO})_2$ and the molecular weight 363.8 g/mol. The CAS number of the complexed compound is 292140-29-5. The theoretical contents of zinc (as Zn(II)) and HMTBa are 17.97% and 82.03%, respectively.

Analytical data of three recent batches were provided by the applicant.⁸ The zinc content ranged from 18.2% to 18.6%; the content of HMTBa ranged from 80.0% to 80.4%. These data show compliance with the new specifications proposed by the applicant.

The measurement of undesirable substances (arsenic (As), lead (Pb), cadmium (Cd), mercury (Hg), dioxins and the sum of dioxins plus dioxin-like polychlorinated biphenyls (PCBs)) was done in three recent batches⁸ of the additive. The results reported were the following: ≤ 0.8 mg As/kg additive, 4.1–5.5 mg Pb/kg additive, 0.22–0.34 mg Cd/kg additive, 0.02–0.03 mg Hg/kg additive, 0.087–0.236 ng WHO-PCDD/F-TEQ/kg and 0.089–0.244 ng WHO-PCDD/F-PCB-TEQ/kg additive. These values are below the threshold set by Directive 2002/32/EC on undesirable substances⁹ for compounds of trace elements or, if not mentioned in the Directive, do not represent a concern.

The nickel content of the additive, analysed in three batches, ranged from 1.54 to 1.64 mg/kg.¹⁰

3.1.2. Physical characteristics of the product

The additive is marketed in the form of a grey-tan powder or granules. Its solubility in water is 1.8% at 25°C. The bulk and tap density of the additive were measured in three batches resulting on an average of 927 kg/m³ and 1,035 kg/m³, respectively.¹¹

The dusting potential of the additive – measured in the same three batches as density – determined by the Stauber–Heubach method was in the range of 165–3,500 mg/m³,¹² thus showing high variability (one batch with dusting potential being one order of magnitude lower than the other two).¹³ Analysis of particle size distribution of the dust, from three additive's batches,¹⁴ resulted on

⁸ Technical Dossier/Supplementary Information_November19/Appendix 2.

⁹ Directive 2002/32/EC of the European Parliament and of the council of 7 May 2002 on undesirable substances in animal feed. OJ L 140, 30.5.2002, p. 10.

¹⁰ Technical Dossier/Supplementary Information_November19/Appendix 1.

¹¹ Technical dossier/Section II/Annex_II_04_Bulk; Annex_II_05_Tap.

¹² Technical dossier/Section II/Annex_II_03_Dusting.

¹³ Technical Dossier/Supplementary Information_November19/Appendix 3.

¹⁴ The results reported refer only to two batches; the applicant argued that in the third batch the dust was very low and did not allow the analysis of particle size distribution.

average in 10.7% (range 10.5–11.0%) of particles < 1 µm and 83.9% (range 80.1–87.8%) < 10 µm. The zinc content of the dust from the same three batches resulted on average in 153.6 mg/kg dust (range 143.3–164.3 mg/kg dust).¹⁵

3.1.3. Stability and homogeneity

The applicant has provided new data to support shelf-life of the additive. Three lots of the additive were stored for at least 5.5 years¹⁶; at the end of the experiment a total of 97.0% and 99.9% of the initial zinc and HMTBa, respectively, was recovered.

Data to support homogeneous distribution of the additive on premixtures were submitted.¹⁷ The study was performed with two premix formulations, Premix-1 and Premix-2 (one lot from each), in which the inclusion of Mintrex[®]Zn was 26.0% and 25.3%, respectively. In both cases, samples from nine bags were taken and the zinc content analysed. The coefficients of variation were 2.9% and 2.5% for Premix-1 and Premix-2, respectively.

3.1.4. Conditions of use

The additive is authorised for all animal species/categories up to the total zinc content in complete feed established in the current legislation:

- Dogs and cats: 200 mg total Zn/kg complete feed
- Salmonids and milk replacers for calves: 180 mg total Zn/kg complete feed
- Piglets, sows, rabbits and all fish other than salmonids: 150 mg total Zn/kg complete feed
- Other animal species and categories: 120 mg total Zn/kg complete feed

The current authorisation includes the following *Other provisions*:

- 1) The additive shall be incorporated into feed in the form of a premixture.
- 2) For user safety: breathing protection, safety glasses and gloves should be worn during handling.

3.2. Safety

The applicant provided data concerning the monitoring of adverse effects of the additive, a literature search and new studies (on safety for the users).

The monitoring of adverse effects was implemented as part of the quality assurance program of the company.

The applicant performed a structured literature search.¹⁹ The sites consulted were LIVIVO and Ovid, sixteen single databases (incl. PubMed and Web of Science), and eight publishers search facilities (incl. Elsevier, Ingenta, Springer, Wiley); the search period covered from 2008 to April 2019. The search terms used, relevant for Mintrex[®]Zn, comprised the active substances/additive and keywords related to the safety/toxicity. The search included also other keywords relevant for Mintrex[®]Cu and Mintrex[®]Mn. It resulted in a total of 394 hits.²⁰ In total nine publications were considered relevant for the assessment of Mintrex[®]Zn.

The relevant findings identified from the data above are described in the respective safety sections below.

3.2.1. Safety for the target species

In its opinion of 2009, the FEEDAP Panel concluded, based on a tolerance study, that Mintrex[®]Zn was safe for chickens for fattening; however, due to limitations identified in that study, the Panel could

¹⁵ Technical Dossier/Supplementary Information_November19/Appendix 4–7.

¹⁶ Technical dossier/Section II/Annex_II_12_Stability.

¹⁷ Technical dossier/Section II/Annex_II_13_Homogeneity.

¹⁹ Technical dossier/Section III/Annex_III_2_Literature_search.

²⁰ The applicant explained that since the renewal of the three applications that he holds were all due for submission on May 2019, a joint literature search for the three additives (Mintrex[®]Cu, Mintrex[®]Mn and Mintrex[®]Zn) was considered to be adequate.

neither extend the conclusion to other poultry categories nor to other animal species (EFSA, 2009). Following that opinion, the applicant submitted new tolerance studies in laying hens, piglets and calves; based on those trials, and on the one already assessed in chickens for fattening, the FEEDAP Panel concluded that Mintrex[®]Zn is safe for all species up to the maximum authorised zinc content in feed (EFSA FEEDAP Panel, 2009).

From the literature search a total of nine studies were identified. These studies were performed in pigs (Liu et al., 2014), chickens for fattening (Yuan et al., 2011; Zhao et al., 2016), laying hens (Manangi et al., 2015; Min et al., 2018), dairy cows (Nemec et al., 2012), heifers (Whitehurst et al., 2014), fish (Savolainen and Gatlin, 2010) and shrimp (Katya et al., 2016). No adverse effects were reported. However, the FEEDAP Panel notes that in these studies the levels of zinc were below the maximum authorised ones, with the exception of the study in shrimp in which the zinc levels tested were approximately 1.4× the maximum authorised level.

Since the additive contains nickel as an impurity, the FEEDAP Panel assessed the impact of nickel on the safety for the target species. If adding 200 mg Zn/kg (dog or cat) feed – the highest maximum total zinc authorised in feed – from the compound under assessment, nickel would be incorporated at 0.4 µg/kg feed.²¹ According to the National Research Council (NRC, 2005), fish and horses are the most sensitive animal species to nickel with a maximum tolerable level (MTL) of 50 mg/kg feed. Considering the background of nickel in feed (i.e. 4 mg/kg dry matter (DM) feed; Nicholson et al., 1999; Van Paemel et al., 2010), the contribution of the additive in the worst-case scenario would be negligible, and in total the amount of nickel in feed would be well below the MTL.

Based on the assessment above, the FEEDAP Panel concludes that Mintrex[®]Zn remains safe for the target species under the authorised conditions of use.

3.2.2. Safety for the consumers

In the first FEEDAP Panel's opinion on the safety of Mintrex[®]Zn, the Panel reviewed a set of toxicological studies and considered that Mintrex[®]Zn does not introduce any additional toxicity effects compared to other sources of dietary zinc (EFSA, 2008). In the subsequent opinion (EFSA FEEDAP Panel, 2009), based on the evaluation of the data submitted on the deposition of zinc in tissue/products from piglets (muscle, liver, kidney, skin/fat), laying hens (eggs) and dairy cows (milk) when these animals were fed Mintrex[®]Zn, the Panel identified that there was no indication that Mintrex[®]Zn would lead to any higher zinc concentration in tissues/products compared to inorganic zinc. Consequently, differences in zinc exposure of the consumer due to the use of Mintrex[®]Zn were not expected. Thus, the FEEDAP Panel concluded that no specific concerns for consumer safety would arise from the use of Mintrex[®]Zn in feed for all species (EFSA FEEDAP Panel, 2009).

The literature search did not identify studies that report tissue levels different from those submitted and discussed previously.

In summary, no additional data have become available that would lead to modify the previous conclusions on the safety of the additive for consumers. Therefore, the FEEDAP Panel concludes that Mintrex[®]Zn remains safe for the consumers under the authorised conditions of use.

3.2.3. Safety for user

In its opinion of 2008, the FEEDAP Panel concluded that Mintrex[®]Zn was safe for the user provided that protective measures are taken (EFSA, 2008). The authorising Regulation establishes that 'breathing protection, safety glasses and gloves should be worn during handling' of the additive.

According to the monitoring report, three customers reported user safety-related incidents during the handling of the additive. The applicant indicated that in two cases the handling of the additive was not done according to the measures stated in the material safety data sheet. In the other case, two users from the same employee developed skin irritation despite wearing gloves and face mask; the specific batch was subjected to an acute dermal irritation/corrosion testing and was found not to be a skin irritant.²² No

²¹ These calculations follow a worst-case scenario by i) considering that all the zinc in the feed comes from the additive, ii) the minimum content of zinc for the additive and iii) taking into consideration the maximum nickel content reported for the additive under assessment.

²² The applicant reported that, as part of the investigation, three separate lots of MINTREX[®]Zn, including the complaint lot, were sent to an external laboratory for Acute Dermal Irritation/Corrosion testing. Results for all three lots indicated that the product is not a skin irritant; erythema (redness) and edema (swelling) were negative over the entire duration of the 72-h test. No other details on the study were provided.

complaints were received from other customers using the same batch. The FEEDAP Panel considers this later incident as a chance effect.

The literature search did not identify relevant studies on the safety of the additive for the users.

The applicant provided new studies on the effects of the additive on the respiratory tract and on skin and eyes, which are described below.

3.2.3.1. Effects on the respiratory system

The applicant provided an acute inhalation toxicity test in rats.²³ The study aimed at determining the potential for Mintrex[®]Zn to produce toxicity from a single exposure via inhalation route (nose-only exposure). The study was good laboratory practice (GLP) compliant and conducted according to OECD Guidelines 403. Under the conditions of this study, the single exposure acute inhalation LC₅₀ of the test substance is greater than 1.04 mg/L in male and female rats.

Data on the product characterisation can be used to derive inhalation exposure, and to re-assess the effects of the additive on the respiratory system. The highest dusting potential of the additive was 3.5 g/m³, and the zinc maximum concentration in the dust was 164.3 mg/kg (see Section 3.1.2). Thus, a maximum concentration of 575 mg Zn/m³ could be released when handling the additive. The respirable fraction of the dust is up to 87.8 %, thus the respirable zinc from the dust is 505 mg/m³. Considering a threshold limit value (TLV) for zinc of 2 mg/m³ (ACGIH, 2015) the TLV is exceeded by two orders of magnitude. Owing to the zinc content of the additive, the FEEDAP Panel considers that handling of the additive poses a risk to users by inhalation.

The highest nickel content analysed in the additive was 1.64 mg/kg (see Section 3.1.1). The highest measured dusting potential of the product was 3.5 g/m³, corresponding to about 0.006 mg Ni/m³,²⁴ which is below the occupational exposure limit (OEL) proposed for the inhalable fraction of water-soluble nickel (0.01 mg Ni/m³; European Commission, 2011). However, due to the sole presence of nickel in the additive, given the well-known sensitizing properties of nickel, Mintrex[®]Zn should be considered as a respiratory sensitiser.

3.2.3.2. Effects on skin and eyes

An acute dermal toxicity test was conducted with rats to determine the potential for Mintrex[®]Zn to produce toxicity from a single topical application.²⁵ The study was conducted under GLP and according to OECD Guideline 402. Under the conditions of this study, the single dose acute dermal LD₅₀ of the test substance is greater than 2,000 mg/kg body weight.

The potential of skin irritancy of the additive was tested in a GLP *in vitro* study performed according to the OECD Guideline 439.²⁶ Under the conditions of this study, Mintrex[®]Zn is considered a non-irritant to skin.

The potential of eye irritancy of the additive was tested in a GLP *in vitro* study performed according to the OECD Guideline 437: Bovine Corneal Opacity and Permeability Test Method.²⁷ Under the conditions of this study, the results were considered inconclusive and based on the classification of UN GHS 'No Prediction can be made'. Thus, the applicant performed a second test to assess the potential eyes irritancy of the additive; the test selected was the *in vitro* EpiOcular[™] eye irritation test (OECD TG 492: Reconstructed human Cornea-like Epithelium Test Method) and the study was done under GLP.²⁸ Under the conditions of this study, Mintrex[®]Zn is not considered an eye irritant (UN GHS: no category).

The nickel content of the additive is up to 1.64 mg/kg; given its well-known sensitisation potential (European Commission, 2011) and in the absence of skin sensitisation studies the additive is considered as a skin sensitiser.

3.2.3.3. Conclusions on the safety for the users

Owing to the zinc and nickel content of Mintrex[®]Zn, the handling of the additive poses a risk to users by inhalation. The additive is not a skin or eye irritant but is considered as a skin sensitiser.

²³ Technical Dossier/Section III/Annex_III_5.

²⁴ Assuming an equivalent distribution of nickel in the dust than that in the additive. (No information of the content of nickel in dust was available).

²⁵ Technical Dossier/Section III/Annex_III_4.

²⁶ Technical Dossier/Supplementary Information_September20/Appendix 1.

²⁷ Technical Dossier/Supplementary Information_September20/Appendix 2.

²⁸ Technical Dossier/Supplementary Information_September20/Appendix 3.

3.2.4. Safety for the environment

In its opinion of 2008, the FEEDAP Panel concluded that Mintrex[®]Zn did not represent additional risks to the environment compared to other sources of zinc which it would substitute (EFSA, 2008).

The literature search did not identify any relevant studies on the safety of the additive for the environment. Thus, there is no new evidence that would lead to modify the Panel's previous conclusion. Therefore, the FEEDAP Panel reiterates that the use of Mintrex[®]Zn in feed does not pose an additional risk to the environment as long as the maximum authorised content in complete feed is not exceeded.

3.3. Efficacy

The present application for renewal of the authorisation does not include a proposal for amending or supplementing the conditions of the original authorisation that would have an impact on the efficacy of the additive. Therefore, there is no need for assessing the efficacy of the additive in the context of the renewal of the authorisation.

3.4. Post-market monitoring

The FEEDAP Panel considers that there is no need for specific requirements for a post-market monitoring plan other than those established in the Feed Hygiene Regulation²⁹ and Good Manufacturing Practice.

4. Conclusions

The additive complies with the new specifications proposed: $\geq 17\%$ Zinc and $\geq 79\%$ (2-hydroxy-4-methylthio)butanoic acid (DL-methionine hydroxy analogue, HMTBa). No mineral oil is used in the manufacturing process. These modifications represent a variation compared to the current authorisation.

The FEEDAP Panel concludes that the use of Mintrex[®]Zn under the current authorised conditions of use remains safe for all animal species, the consumers and the environment.

The FEEDAP Panel concludes that, owing to the zinc and nickel content of Mintrex[®]Zn, the handling of the additive poses a risk to users by inhalation. The additive is not a skin or eye irritant but is considered as a skin sensitiser.

There is no need for assessing the efficacy of the additive in the context of the renewal of the authorisation.

5. Documentation as provided to EFSA/Chronology

Date	Event
08/05/2019	Dossier received by EFSA. Dossier Zinc chelate of hydroxy analogue of methionine (MINTREX [®] Zn). Submitted by Novus Europe S.A./N.V
23/05/2019	Reception mandate from the European Commission
09/07/2019	Application validated by EFSA – Start of the scientific assessment
20/09/2019	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. <i>Issues: characterisation</i>
09/10/2019	Comments received from Member States
14/11/2019	Reception of supplementary information from the applicant - Scientific assessment re-started
10/12/2019	Request of supplementary information to the applicant in line with Article 8(1)(2) of Regulation (EC) No 1831/2003 – Scientific assessment suspended. <i>Issues: safety for the users</i>
18/09/2020	Reception of supplementary information from the applicant - Scientific assessment re-started
18/11/2020	Opinion adopted by the FEEDAP Panel. End of the Scientific assessment

²⁹ Regulation (EC) No 1831/2003 of the European Parliament and of the Council of 22 September 2003 laying down requirements for feed hygiene. OJ L 35, 8.2.2005, p. 1.

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Abbreviations

CAS	Chemical Abstracts Service
DM	dry matter
EFSA FEEDAP Panel	EFSA Panel on Additives and Products or Substances used in Animal Feed
EURL	European Union Reference Laboratory

HMTBa	DL-methionine hydroxy analogue
LC ₅₀	lethal concentration, median
LD ₅₀	lethal dose, median
MTL	maximum tolerable level
OECD	Organisation for Economic Co-operation and Development
OEL	occupational exposure limit
PCB	polychlorinated biphenyls
PCDD/F	polychlorinated dibenzo- <i>p</i> -dioxins and dibenzofurans
TEQ	toxic equivalent
TLV	threshold limit value
WHO	World Health Organization