S & C BEST
TOXICOLOGY

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Toxicological evaluation and Tolerable Daily Intake derivation of Bismuth

Summary

1. Goals

The goal of the present paper is a human toxicological evaluation of Bismuth, in order to derive its Tolerable Daily Intake (TDI), to be eventually used in a risk assessment of this substance in materials in contact with food.

2. Summary and conclusion

Based on available toxicological data on Bismuth, it is not mutagenic, not carcinogen and not toxic to reproduction. Several data are available, indicating that insoluble bismuth compounds are related to low toxicity, whereas soluble bismuth organic compounds such bismuth subcitrate are associated with higher toxicity, probably due to the enhanced uptake of soluble bismuth salts in human bodies after ingestion.
In the present report, the self-derived oral Tolerable Daily Intake (TDI) is derived from the most reliable and conservative toxicological data reported in SCCS opinion for Bismuth Citrate, which is a water-soluble bismuth salt. The **self-derived TDI** is established at **0.08 mg/kg bw/day**. This value was derived according to FCA 2020 guideline and corresponds to an oral safe level of 4.8 mg/person/day, for an adult of 60 kg standard body weight.

3. General approach

3.1 Substances with available experimental toxicological data

The present toxicological evaluation has been conducted according to EFSA, 2019 and FCA, 2020. For the substances with available experimental toxicological data, the self-derived TDI (sTDI) is calculated from the most relevant toxicological data (Point of Departure or PoD), by applying the Uncertainty Factors (UF) described in FCA 2020.

I. Initially, it shall be demonstrated that the substance does not pose any concern with regard to genotoxicity
II. Then, an appropriate dose descriptor from repeated dose (chronic/subchronic/subacute) toxicological studies can be selected. This dose descriptor or Point of Departure (PoD) can be a NOAEL, a LOAEL or BMD-L. In some cases, developmental endpoints may provide the most sensitive PoD for risk assessment. Yet, it should be noted that the NOAELs for parental toxicity in OECD 414, OECD 416 or OECD 443 studies usually do not provide a preferable PoD, as the examination typically does not include important parameters used for the assessment of systemic toxicity. Therefore, these should only be used if they provide the most sensitive PoD.
III. Then, the self-derived Tolerable Daily Intake (sTDI, expressed as mg/kg bw/day) can be derived from the PoD, by applying the Uncertainty Factors (UF) described in FCA 2020. Those UFs are:
    i. UF interspecies/intraspecies: this UF is set to be 100, to give a margin of safety to consider the possibility that humans may be more sensitive than animals and that some humans may be more sensitive than others.
    ii. UF study duration: a factor of 2 is sufficient to extrapolate from a high-quality 90-day (subchronic) study to chronic exposure conditions. 28-day studies may also be used and a factor of 6 is applied. As for reproductive/developmental toxicity studies, a factor equal to 1 is selected when the most conservative toxicological data is taken from a dose descriptor established in F1 or, when available, F2 generations.
    iii. UF LOAEL: a factor up to 10 may be applied, based on expert judgement
    iv. UF data gap/read across: when available testing information is insufficient to provide information necessary for a food contact safety assessment, additional uncertainty factors may be applied, i.e., when read across approach is applied, in absence of toxicological data of the substance under evaluation

The derivation of the sTDI is performed as follows:

sTDI (mg/kg bw/day) = PoD (mg/kg bw/day) / UFs

The toxicological data to select the PoD were searched in the following public databases:

- PubChem (https:// http://www.pubchem.com/): databases on toxicology, hazardous chemicals, environmental health, and toxic releases. This database reports also the data from HSDB and ToxNet as from 1st of January 2020
- ECHA (https://echa.europa.eu/it/home): provides information of substances registered under REACH (i.e. hazardous properties, classification and labelling and precautions for use).
- EFSA (https://www.efsa.europa.eu/): contains the scientific opinion on food ingredients or additives or food contaminants.
- OECD Existing Chemicals Database: it contains all documents associated with the final published assessment (profiles, assessment reports and dossiers) for a given compound.
- CIR, Cosmetic Ingredient Review (https://www.cir-safety.org/). It contains relevant studies on cosmetic ingredients;
- IARC (https://www.iarc.who.int/):The International Agency for Research on Cancer (IARC) is the specialized cancer agency of the World Health Organization.
  The objective of IARC is to promote international collaboration in cancer research.

4. Toxicological profile of Bismuth

Molecular weight: 208.98040 g/mol

Notification for Classification and Labelling:

- H413: May cause long lasting harmful effects to aquatic life

General information:

- Bismuth atom is a pnictogen and a metal atom. It is used in cosmetics, pigments; and in a few pharmaceuticals, (e.g. bismuth subsalicylate, used to treat diarrhea) (PubChem, 2024).
- Bismuth, the most metallic and the least abundant of the elements in the nitrogen group (Group 15 [Va] of the periodic table). Bismuth is hard, brittle, lustrous, and coarsely crystalline. It can be distinguished from all other metals by its colour—gray-white with a reddish tinge. Bismuth is about as abundant as silver, contributing about 2×10^{-5} weight percent of Earth's crust (Britannica, 2024).
- Food represents the main source of bismuth intake in the general population. It is also found in certain medications. Current publication describes derivation of blood and urine biomonitoring equivalents (BEs) for bismuth. Derived BEs can be used as screening tools for interpreting population biomonitoring data for bismuth. The toxicity database for bismuth is fairly limited, which may be due to the fact that bismuth is considered a relatively low toxic metal, especially resulting from low bioavailability (and thus systemic absorption) following oral dosing (Poddalgoda et al., 2020).
- Bismuth is considered the safest of heavy metals primarily because of the low solubility of many bismuth salts: It exists in trivalent and pentavalent oxidation states (the trivalent being more abundant and stable) and forms soluble and insoluble, organic and inorganic salts. In general, insoluble salts such as bismuth citrate and carbonate are of low toxicity; neurotoxic effects are associated predominantly with the lipid soluble organic salts (e.g. bismuth subgallate); renal toxicity is associated with the water-soluble organic compounds eg bismuth sodium triglycollamate, bismuth subsalicylate and bismuth sodium tartrate (SCCS, 2013).

Exposure data:

- Bismuth occurs naturally as a free metal or in combined forms, such as bismite (bismite oxide) and bismuthite (bismuth sulfide), which is commonly associated with sulfide ores of lead, copper and tin dioxide. Being a natural element, humans are exposed to bismuth primarily through diet, with background exposures estimated between 5 and 20 µg/day (0.07 and 0.29 µg/kg bw/day, assuming a body weight of 70 kg). According to a Total Diet Study (TDS) in Canada, average dietary intakes for Canadians (males and females of all ages) was 0.01 µg/kg bw/day with the highest intake in 4–6 months age group at 0.101 µg/kg bw/day (Poddalgoda et al., 2020).

- Patients suffer toxicity at different bismuth levels in blood but the syndrome is rare when bismuth levels are below 50 mg/L. Among the bismuth-based regimens, the use of insoluble bismuth compounds such as bismuth oxychloride and bismuth carbonate are related to low toxicity, whereas the use of soluble bismuth organic compounds such as bismuth sodium tartrate and tripotassium dicitratobismuthate (also called bismuth subcitrate), or the combined use of bismuth with thiolate-containing ligands, are associated with high toxicity, such as neurotoxicity and nephrotoxicity. This is probably due to the enhanced uptake of soluble bismuth salts in human bodies. It has also been suggested that the oral bismuth drugs need to undergo methylation by intestinal microbes to enable them to be absorbed. Absorbed bismuth will accumulate in the kidneys, lungs, spleen, liver, brain, and muscles, and will be eliminated in urine and feces via bile and intestinal secretions (Wang et al., 2019).

Toxicokinetics:

- Acute or chronic administration of therapeutic compounds with significantly high concentrations of bismuth have been attributed to a number of toxic effects, including nephropathy, encephalopathy, osteoarthropathy, gingivitis, stomatitis, colitis and hepatitis. Most of the available data are based on case studies on bismuth induced encephalopathy and nephrotoxicity. In general, the available database for bismuth-induced toxicity is relatively old (e.g. encephalopathy data are from 1970's). Conversely, some recent publications have also reported encephalopathy or nephrotoxicity in certain individuals, who consumed large doses of over the-counter bismuth-containing medications. Bismuth-induced encephalopathy is often associated with chronic overexposure, whereas nephrotoxicity is generally reported for acute overdosing. In addition, different therapeutic compounds appeared to be responsible for different bismuth-related toxic effects. In most cases, bismuth-induced toxicity effects are reversible after discontinuation of exposure. It should be noted that these toxic effects are rarely seen with normal use of bismuth compounds because systemic absorption of bismuth through the gastrointestinal tract is significantly low (Poddalgoda et al., 2020).
- There are some publications that allow an assessment of the oral bioavailability of bismuth metal in rats, which are however somewhat of age. In the following, the results from two review articles that were considered to contain relevant and reliable data are summarized:

  Systemic bioavailability from bismuth compounds such as tripotassium dicitrato bismuthate (De-Nol), bismuth subsalicylate and ranitidine bismuth citrate is low. Less than 1% of the bismuth dose administered is absorbed.

  The normal concentration of bismuth in blood is between 1 and 15µg/L, but absorption from oral preparations produces a significant rise. Transient peak plasma bismuth concentrations greater than 50 µg/L are observed 30-60 minutes after dosing with tripotassium dicitrato bismuthate in some patients but are not associated with any toxic effects.

  The distribution of bismuth in the organs is largely independent of the compound administered: the concentration in kidney is always the highest. Elimination from the body takes place by the urinary and faecal routes. Elimination from blood displays multi-compartment pharmacokinetics. After discontinuation of treatment with bismuth preparations its excretion in urine may continue for up to 3 months, by which time blood bismuth concentrations have declined to pre-treatment values.

  In conclusion, the assumption appears justified that upon oral uptake the systemic uptake is low for bismuth. An oral absorption factor of 1% will be taken forward for risk characterization purposes as a conservative assumption (ECHA, 2024).

  No data on inhalation absorption and distribution are available for bismuth metal or bismuth compounds. Considering the very low oral bioavailability and the minimal predicted deposition in the respiratory tract, it is proposed to take forward an inhalation absorption factor of 1% for the purpose of risk characterization, thus rendering corrections when extrapolating route-to-route (oral-inhalation) unnecessary (ECHA, 2024).

  In the absence of measured data on dermal absorption, previous guidance primarily directed at organic chemicals with a defined lipophilicity and corresponding percutaneous transfer potential, suggests the assignment of either 10% or 100% default dermal absorption rates. In contrast, the currently available scientific evidence on dermal absorption of metal cations (predominantly based on the experience from previous EU risk assessments) yields substantially lower figures, which can be summarized briefly as follows:

  Measured dermal absorption values for metal cations or inorganic metal substances in studies corresponding to the most recent OECD test guidelines are typically 1 % or even less. Therefore, the use of a 10 % default absorption factor

is not scientifically supported for such ionic species. This is corroborated by conclusions from previous EU risk assessments (Ni, Cd, Zn), which have derived dermal absorption rates of 2 % or far less (but with considerable methodical deviations from existing OECD methods) from liquid media.

However, considering that under industrial circumstances many applications involve handling of dry powders, substances and materials, and since dissolution is a key prerequisite for any percutaneous absorption, a factor 10 lower default absorption factor may be assigned to such "dry" scenarios where handling of the product does not entail use of aqueous or other liquid media. This approach was taken in the in the EU RA on zinc. A reasoning for this is described in detail elsewhere, based on the argument that dermal uptake is dependent on the concentration of the material on the skin surface rather than its mass.

Consistent with the methodology proposed in HERAG guidance for metals (HERAG fact sheet - assessment of occupational dermal exposure and dermal absorption for metal cations and inorganic metal substances; EBRC Consulting GmbH / Hannover /Germany; August 2007), the following default dermal absorption factors for metal cations have therefore been proposed (reflective of full-shift exposure, i.e. 8 hours):

  - From exposure to liquid/wet media: 1.0 %
  - From dry (dust) exposure: 0.1 %

- Glutathione (GSH) may play a vital role for bismuth metabolism and detoxification in mammalian cells. Bismuth ions were found to be passively absorbed, conjugated to GSH and then transported into vesicles via MRP transporter; the sequestration of absorbed bismuth consumes cytosolic glutathione and activates the *de novo* biosynthesis, which in turn facilitated passive uptake of bismuth. The self-propelled positive feedback cycle actively eliminated bismuth from both intra- and extracellular space, thus protecting critical systems of human body from acute toxicity. Considering that GSH is ubiquitous in most living cells, but absent in certain anaerobic or microanaerobic bacteria such as H. pylori, the GSH and MRP mediated self-propelled disposal of bismuth in host cells might be accountable for the selective toxicity of bismuth drugs (Wang et al., 2019).
- Despite the large variation in bismuth compounds used in human and animal studies, the data on distribution of the metal in tissues are in close agreement. The highest concentration is always found in the kidneys, where retention is also longer than other tissues - in the rat, 144 hours after injection of bismuth citrate (206Bi), 12% of injected dose remained in the kidney, 0.9% in the bone, but little or no levels were detected in other organs (Slikkerveer and de Wolff, 1989).
- Because newborn animals from bismuth-treated mothers show the same concentration as adults, it is inferred that bismuth passes into the placental circulation. Bismuth is also excreted into the milk, but in lower concentrations than into the urine (Beliles, 1994).

Acute toxicity:

- Bismuth metal is not acutely toxic via oral route since in an acute oral toxicity test in rats with bismuth, the LD50 was determined to be > 2000 mg/kg bw (ECHA, 2024).
- For the acute inhalation toxicity study in the rat with bismuth metal powder, it was not possible to generate a stable aerosol atmosphere with a mass median aerodynamic diameter of < 4 um with the supplied test item as required by the OECD guideline for the testing of chemicals 436. Due to the high density, the coarse nature of the particles and the low tendency of the test item to become airborne, the conduction of an acute inhalation toxicity test was shown to lack technically feasibility. Thus, according to section 8.5.2, column 2, annex VIII of regulation (EC) 1907/2006 further testing is not required (ECHA, 2024).
- One acute dermal toxicity study was conducted in 10 albino rabbits with a bismuth Grecian formula (0.5% bismuth citrate) showing an LD50 greater than 2 g/kg bw (SCCS, 2013).

Irritation:

- Bismuth metal is not considered to be irritating to skin or to the eye. The results of an available *in vitro* skin irritation study (human skin model) with dibismuth trioxide indicate that bismuth is not irritating to skin by read across. Results of an available *in vivo* eye irritation study (rabbits) with dibismuth trioxide indicate that bismuth is not irritating to eyes by read across (ECHA, 2024).
- The test formulations already at 0.5% Bismuth citrate showed skin and eye irritation potential; however, the conclusion from these studies are not considered valid due to lack of key information (identity and characterization of the test substance) (SCCS, 2013).

Sensitization:

- No data about the sensitization properties of bismuth metal are available. In a guideline study with the more bioavailable substance, bismuth hydroxide nitrate oxide, the sensitizing potential was determined in the LLNA in mice. Results show that bismuth hydroxide nitrate oxide does not reveal any sensitizing properties and should not be classified and labelled according to regulation (EC) No.1272/2008 (ECHA, 2024).

Repeated dose toxicity:

- Bismuth (Mean particle diameter: 10 µm - Storage condition of test material: at room temperature - Purity: 99.9%) was administered to rats via oral route for 28 days at doses equal to 40, 200, 1000 mg/kg bw/day. There were no significant changes attributed to treatment with bismuth on clinical signs, body weights, food consumption, haematology, clinical chemistry, urinalysis, organ weights, necropsy, or histopathological findings in the 28-day repeated oral dose toxicity study. As a result of the findings, the NOAEL of bismuth was determined to be 1000 mg/kg for males and females (ECHA, 2024).
- The oral (gavage) administration of Bismuth Subnitrate to male and female rats at dose levels up to 1000 mg/kg bw/day was well tolerated in an OECD 408 study with additional reproductive toxicity endpoints. There was no adverse effect of treatment on body weight development and dietary intake in animals of either sex. Hematology, blood chemistry, testosterone hormone assessment, estrus cycle assessment in females, sperm analysis in males and microscopic examination of the selected tissues did not identify any findings of toxicological relevance. A dose level of 1000 mg/kg bw/day is therefore considered to be the NOAEL for systemic toxicity within the confines of this type of study (ECHA, 2024).
- In an OECD 408 study in rats via oral route at 0, 30, 300, 1000 mg/kg bw/day, the NOAEL was set at 30 mg/kg bw/day, based on ingesta-filled caeca and nasal histopathology changes at 300 and 1000 mg/kg/day. According to SCCS, as the bismuth species systemically available is/are unknown and systemic bismuth is considered the toxic agent, a NOAEL of 16 mg/kg bw/day for bismuth (corresponding to 30 mg Bismuth citrate per kg bw/day) could be used for the calculation of the MoS (SCCS, 2013).

Genotoxicity:

- No data about genetic toxicity of bismuth metal are available. There are publications available in which soluble bismuth salts were tested. There is no indication for genotoxic/mutagenic effects of either colloidal bismuth subcitrate, bismuth subsalicylate or bismuth nitrate in these available publications. In addition, in an available guideline study with the soluble bismuth hydroxide nitrate oxide no gene mutation potential was determined in the hprt locus of mouse lymphoma cells. Bismuth hydroxide nitrate oxide should not be classified and labelled according to regulation (EC) No.1272/2008.

  Due to the fact that soluble bismuth compounds are not mutagenic, it can be considered that bismuth metal as a poorly soluble substance (resulting in a lower bioavailability) is not mutagenic or genotoxic and should not be classified as such.

  Based on available data from publications and on experimental results with bismuth hydroxide nitrate oxide, bismuth metal does not need to be classified for genetic toxicity (ECHA, 2024).

Carcinogenicity:

- For bismuth metal, no data from carcinogenicity studies are available. Bismuth is of low systemic toxicity, there is no evidence from repeated dose studies that the substance induces hyperplasia and/or pre-neoplastic lesions, and bismuth can be considered to be of generally low bioavailability (< 1% via oral, dermal and inhalation routes). Finally, bismuth metal is neither legally classified as laid down in Annex I of Directive 67/548/EC nor do any other available data currently suggest any classification. In conclusion, the registrant is of the opinion that such study must not be proposed (ECHA, 2024).
- Some bismuth compounds have been studies in long term studies with rats and mice and none of the studies reported tumor induction by bismuth compounds (SCCS, 2013).

Toxicity to reproduction:

- In the OECD 408 study conducted in rats, the NOAEL set for reproductive toxicity is 1000 mg/kg bw/day (ECHA, 2024).
- The histochemical silver amplification technique auto-metallography was used to trace bismuth in the testis of Wistar rats after i.p. administration of bismuth subnitrate. Groups of 4 male Wistar rats were treated with an overdose of 500 mg/kg bismuth subnitrate intraperitoneally and allowed to survive for 2 weeks and 8 weeks, respectively. A group

of four rats served as control and received an intraperitoneal injection of 0.9% saline. The reason for choosing this high dose was that bismuth subnitrate is rather insoluble, and very high doses of bismuth subnitrate are needed to get bismuth into the bloodstream, compared to other bismuth compounds. In both treatment groups, in the seminiferous tubules, bismuth was located in lysosomes of Sertoli cells. Leydig cells showed large amounts of AMG-bismuth in their lysosomes pointing at a possible effect of bismuth on testicular function and male reproductive capability.

- Studies have demonstrated that bismuth overdose results in a lowered serum testosterone level but the mechanisms involved are unknown. The effect of bismuth subnitrate was therefore investigated on Leydig cells isolated from rats. 10 male Wistar rats were treated with one intraperitoneal injection of 500 mg/kg bismuth subnitrate and allowed to survive for 2 weeks. 10 rats served as control and received an intraperitoneal injection of 0.9% saline. Under the experimental conditions applied, bismuth was observed in Leydig cells, with a subsequent reduction in serum testosterone levels. Stereological procedures were used to estimate the number of Leydig cells in the right testis from retained rats used in a previous study. The mean number of Leydig cells in the control group was estimated to be 18.7 x 10^6, which was comparable to previous estimations. In the group exposed to bismuth, the mean was 15.5 x 10^6. The observed 17% difference between the two groups was statistically significant. The inter-individual variation was largest in the bismuth-exposed group. Testis weight and body weight were not significantly reduced after bismuth exposure. No signs of overt toxicity were observed but a reduction in the number of Leydig cells in testes was demonstrated. These findings support the hypothesis that bismuth has a direct toxic effect on rat Leydig cells under the experimental conditions used and suggests a potential risk of bismuth to male reproduction. According to SCCS, the study data suggest that high internal doses of bismuth achieved by intraperitoneal application may lead to damage of Leydig cells and consequently serum testosterone levels may be reduced compared with controls. The data shows a potential hazard to male reproduction at high internal doses that may also be otherwise toxic. Any conclusions on risk assessment of male fertility and reproduction with regards to bismuth citrate or other bismuth species formed after dermal or oral absorption are not possible on the basis of such studies (SCCS, 2013).

Developmental toxicity:

- In an OECD 414 Bismuth Citrate was administered to pregnant rats via oral route at doses equal to 100, 300, 1000 mg/kg bw/day. All the doses were well tolerated. The NOEL for maternal toxicity was considered to be 100 mg/kg bw/day, based on reductions in body weight/body weight gain at 300 and 1000 mg/kg bw/day. No treatment-related changes were detected in the offspring parameters measured. The NOEL for developmental toxicity, was therefore, considered to be 1000 mg/kg bw/day (SCCS, 2013).

Human data:

- The effects of bismuth toxicity on the kidney – the main organ responsible for blood filtration—were systematically reviewed, motivated by availability of several sources of bismuth in contact with humans including environmental, medications, dental materials, and cosmetics, potentially leading to kidney filtration of this chemical. No previous studies have systematically reviewed the literature considering this association. The review included studies publication dates ranged from 1961 to 2021 and the countries of publication were the United States of America, United Kingdom, Germany, Turkey, Switzerland, and Canada. Bismuth sources affecting the kidneys were uniquely reported as from medical purposes and mostly associated to overdoses with several symptoms, apparently with dose-dependent consequences. Patient history of renal impairment seemed to affect the outcome of the case. Several therapies were conducted following bismuth intoxication, and few studies performed renal biopsies describing its histological findings. It is crucial to reconsider the nephrotoxicity of bismuth compounds, mainly in patients with previous history of renal impairment (Pelepenko et al., 2022).

Other data:

- Overdosing of Bismuth subcitrate (CBS), used to treat peptic ulcers and H.Pylori infections, has been reported to result in serious, though reversible, nephrotoxicity in humans. However, little is known about the nature of renal damage induced by bismuth (Bi). Single large oral CBS doses (0.75, 1.5 and 3.0 mmol Bi/kg) were administered to three groups of female rats. The highest dose caused kidney damage (proteinuria, glucosuria, elevated plasma urea and plasma creatinine levels; full recovery within 10 days). The medium dose caused the same effects, but recovery was within 48 hours, while the lowest dose caused no changes (Leussink et al., 2001).

Safe levels:

- No risk assessments have been conducted to establish exposure guidance values for bismuth. US FDA (2019) has recommended daily intake (RDI) of 200–400 mg up to 4 times daily of bismuth subgallate, which is a deodorant drug product for internal use as an aid to reduce odor from a colostomy or an ileostomy (Bismuth subgallate (C7H5BiO6, mw =394 g/mol- 53% bismuth, by mass). Therefore, the US FDA's recommended intake of 400 mg up to 4 times daily equates to a daily intake of 848 mg of bismuth. Assuming a standard adult body weight of 70 kg, this equates to 12.1 mg bismuth/kg/day (i.e. RDI). The US FDA's RDI for bismuth subgallate can be used as a surrogate for the screening health risk of bismuth exposure, as there is an absence of health-based guidance values for the general population.

5. Derivation of the Tolerable Daily Intake

Despite the broad literature data about effects of bismuth, only few bismuth species are properly quantitatively characterized: often the adverse effects from clinical data are correlated to the bismuth concentration in the blood, which is not a Point of Departure for the Tolerable Daily Intake derivation. Literature also indicates that insoluble bismuth compounds are related to low toxicity, whereas soluble bismuth organic compounds are associated with higher toxicity, probably due to the enhanced uptake of soluble bismuth salts in human bodies after ingestion.
For the calculation of the Tolerable Daily Intake (TDI) of Bismuth, the selected Point of Departure is the most conservative toxicological data listed above, and proposed by SCCS for the water soluble organic salt bismuth citrate: a NOAEL equal to 30 mg/kg bw/day, from an OECD 408 (90 days repeated dose toxicity study) conducted in rats via oral route. Considering that Bismuth weighs ca. 209 g/mol, and citrate ion weighs 172 g/mol, SCCS calculated a NOAEL for Bismuth (ion) equal to 16 mg/kg bw/day.
From this NOAEL, the TDI was calculated hereby by applying the assessment factors described in FCA 2020.

PoD: oral, rat, OECD 408, NOAEL = 16 mg/kg bw/day

UF interspecies / intraspecies	100
UF study duration	2 (subchronic exposure)
UF NOAEL- LOAEL	1
Overall adjustment factor	200

sTDI = 16 mg/kg bw/day / 200 = **0.08 mg/kg bw/day**

A sTDI of 0.08 mg/kg bw/day is equal to a safe level of 4.8 mg/person/day, for a person of 60 kg bw.
This is rather conservative value, because started from the most conservative Point of Departure found in literature.

6. Abbreviations

ADI	Acceptable Daily Intake. This is an estimate of the amount of a substance in food or drinking water that can be consumed daily over a lifetime without presenting an appreciable risk to health. It is usually expressed as milligrams of the substance per kilogram of body weight per day and applies to chemical substances such as food additives, pesticide residues and veterinary drugs.
BEs	Biomonitoring Equivalents
bw	body weight
ECHA	European Chemical Agency
FDA	Food and Drug Administration
GSH	Glutathione
LOAEL	Lowest Observed Averse Effect Level
NOAEL	No Observed Averse Effect Level
NOEL	No Observed Effect Level
PoD	Point of Departure
RDI	Recommended Daily Intake
SCCS	Scientific Committee on Consumer Safety
TDI	Tolerable Daily Intake. This is an estimate of the amount of a substance in food or drinking water which is not added deliberately (e.g contaminants) and which can be consumed over a lifetime without presenting an appreciable risk to health.
TDS	Total Diet Study
UF	Uncertainty Factor

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The present report assessment and conclusion are based on the information available at the day of the below signature.

Place and date, name and signature of the Toxicologist performing the assessment

Portogruaro, 18 July 2024

Author: *Dott. Alessia Sguazzin – Regulatory Toxicologist, S & C BEST S.r.l.*

Signature 

Reviewer: *Dr. Cusan Claudia – European Registered Toxicologist, Founder and Principal Toxicologist at S & C BEST S.r.l.*

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