MICHIGAN DEPARTMENT OF ENVIRONMENT, GREAT LAKES, AND ENERGY

INTEROFFICE COMMUNICATION

TO: File for Lithium Bis(trifluoromethane sulfonyl)imide (CAS No. 90076-65-6)

FROM: Mike Depa, Air Quality Division

DATE: March 23, 2023

SUBJECT: Screening Level for Lithium Bis(trifluoromethane sulfonyl)imide

There are two Initial Threshold Screening Levels (ITSLs) for lithium bis(trifluoromethane sulfonyl)imide (LiTFMSI) (CAS No. 90076-65-6):

Acute ITSL: 40 µg/m³ with a 24-hr. averaging time, and
Chronic ITSL: 1 µg/m³ with an annual averaging time.

The literature was searched to find relevant data to assess the toxicity of LiTFMSI. The following references or databases were searched: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS), Registry for Toxic Effects of Chemical Substances (RTECS), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values (TLVs), National Institute for Occupational Safety and Health (NIOSH) Recommended Exposure Levels (RELs), International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) SciFinder (searched 23 February, 2023), U.S. EPA CompTox, California Office of Environmental Health Hazard Assessment (OEHHA), the U.S. Department of Health and Human Services Agency for Toxic Substances and Disease Registry (ATSDR), European Chemical Agency (ECHA), and the U.S. National Toxicology Program (NTP).

From Wikipedia (2023)

> Lithium bis(trifluoromethanesulfonyl)imide, often simply referred to as LiTFMSI, is a hydrophilic salt with the chemical formula LiC2F6NO4S2. It is commonly used as Li-ion source in electrolytes for Li-ion batteries as a safer alternative to commonly used lithium hexafluorophosphate.
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> Because of its very high solubility in water (> 21 mol), LiTFMSI has been used as a water-in-salt electrolyte for aqueous lithium-ion batteries.

As proposed by Gaines et al. (2023), LiTFMSI is listed as a Per- and Polyfluoroalkyl Substance (PFAS) by EPA in the CompTox database (CompTox, 2022) because it has greater than 30% fluorine atoms (excluding hydrogen) (i.e., F6/F6+C2+Li+N+O4+S2 × 100% = 38%).

Molecular Structure of LiTFMSI:

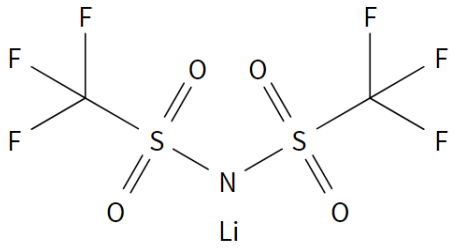

Table 1. Chemical and Physical Properties of LiTFMSI*

Property	Predicted Median	Unit
Molecular Weight	288.10	g/mole
Water Solubility	1730	g/L @ 20 °C
Boiling Point	208	°C
Melting Point	115	°C
Vapor Pressure	0.270	mmHg
Henry's Law	3.13E-5	atm-m^3/mole

* CompTox, 2023 and ECHA, 2023

LiTMSI is considered stable, as the hydrolysis at pH 4, 7 and 9 was lower than 10% after 5 days. Its half-life at 25°C was greater than 1 year (ECHA, 2023).

There was 9% biodegradation after 28 days, in an inherent aerobic biodegradation study (Organization for Economic Cooperation and Development (OECD) Method 302B) and 3% biodegradation after 28 days in a readily biodegradation study (301C). Results in both studies showed that LiTFMSI is not biodegradable (ECHA, 2023).

Toxicity Studies

Genetic Toxicity

Five strains of bacteria Salmonella typhimurium: TA1535, TA1537, TA98, TA100 and TA102 and one strain of Escherichia coli: WP2 uvrA were used to evaluate LiTFMSI in an in-vitro genetic toxicity study (ECHA, 2023). Each strain was exposed to five dose-levels of LiTFMSI (three plates/dose-level). After 48 to 72 hours of incubation at 37°C, the revertant colonies were scored. Evaluation of the toxicity was performed based on observation of the decrease in the number of revertant colonies and/or thinning of the bacterial lawn. The test item LiTFMSI was dissolved in distilled water. Under these experimental conditions, the test item LiTFMSI does not show mutagenic activity in the bacterial reverse mutation test with Salmonella typhimurium and Escherichia coli.

In an in vitro mammalian chromosome aberration test human lymphocytes were exposed to LiTFMSI at various dose levels with and without activation (ECHA, 2023). LiTFMSI did not induce chromosome aberration in culture human lymphocytes.

Corrosivity

A skin irritation study was performed with the LiTFMSI in rabbits (ECHA, 2023). The test item was applied on clipped skin for 4 hours under semi-occlusive coverage. After the exposure period, the bandages were removed, and the test sites were washed using lukewarm tap water and disposable paper towels. LiTFMSI was removed from the test sites as thoroughly as possible without irritating the skin. Thirty minutes following removal of the LiTFMSI, the degree of erythema and edema was read according to the Draize technique. Subsequent examinations were made at 24, 48, 72 and 96 hours and at 7 and 14 days after patch removal. For erythema score, the mean on 3 animals at 24, 48 and 72 hours was 3 with necrosis, and the edema score was 2.33 (see Table 2). Under these conditions, LiTFMSI is considered corrosive to skin (ECHA, 2023).

Table 2. Skin Testing Results

		Hours					Days	
Effect	Rabbit	4	24	48	72	96	7	14
Erythema	Animal 1	3AB	3N	3N	3N	3N	3N	3N
	Animal 2	3N	3N	3N	3N	3N	3N	4N
	Animal 3	3AB	3N	3N	3N	4N	4N	4N
Edema	Animal 1	4	2	2	2	2	2	2
	Animal 2	4	3	3	3	2	2	3
	Animal 3	4	2	2	2	2	2	2

A - Subcutaneous hemorrhage
B - Blanching
N - Possible necrotic area

Sensitization

The potential of the test item LiTFMSI to induce delayed contact hypersensitivity was evaluated in guinea pigs according to the OECD No. 406 and EC B.6 guidelines and in compliance with the principles of Good Laboratory Practice Regulations (ECHA, 2023). Thirty Hartley guinea pigs were allocated to two groups: a control group of five males and five females and a treated group of ten males and ten females. On day 1, three pairs of intradermal injections were performed in the interscapular region of all animals, with control animals receiving vehicle and dosed animals receiving LiTFMSI. On day 8, the LiTFMSI (treated group) or the vehicle (control group) was applied topically to the same site, which was then covered by an occlusive dressing for 48 hours. On day 22, all animals of both groups were challenged by a cutaneous application of the test item to the right flank. The left flank served as control and received the vehicle only. LiTFMSI and vehicle were maintained under an occlusive dressing for 24 hours. Skin reactions were evaluated approximately 24 and 48 hours after removal of the dressing. As equivocal cutaneous reactions were noted, a second challenge application of LiTFMSI was performed on day 40 using the original treated group and a new control group of ten animals (five males and five females) which were free from any previous treatment. The second challenge application was performed under the same experimental

conditions as for the first one, except that the test item and vehicle were applied to the left and right flanks, respectively.

Test item concentrations were as follows:

Induction (treated group)
- intradermal injections (day 1): LiTFMSI at the conc. of 0.1% (w/w) in 0.9% NaCl.
- topical application (day 8): LiTFMSI at the conc. of 50% (w/w) in 0.9% NaCl.

First challenge (all groups)
- topical application (day 22): LiTFMSI at the conc. of 50% (w/w) in 0.9% NaCl.

Second challenge (all groups)
- topical application (day 40): LiTFMSI at the conc. of 10% (w/w) in 0.9% NaCl.

At the end of the study, animals were killed without examination of internal organs. Skin samples were taken from the challenge application sites of the animal showing skin reactions. No histological examination was performed. No clinical signs and no deaths were noted during the main study.

After the first challenge application:
In the control group, at the 24-hour reading, a discrete or moderate erythema was observed in 9/10 animals; a dryness of the skin, marked enough to mask evaluation of erythema in 1/10 animals, was noted in all the animals. In the treated group, a discrete to severe erythema was noted in 19/20 animals. A dryness of the skin was recorded in all the animals. At 48-hour reading, a discrete or moderate erythema was observed in all the animals of the control group and a discrete to severe erythema was noted in all the animals of the treated group. A dryness of the skin, sometimes associated with edema and/or brownish area was recorded in most of the animals of both groups.

After the second challenge application:
In the animals of the control group, no cutaneous reactions were observed at both readings. In the treated group, only a discrete erythema, in addition to dryness of the skin and a brownish area at the 48-hour reading, was noted in 1/20 animals, at both readings. The cutaneous reactions observed in 1/20 animals of the treated group, which were of higher incidence and severity than those recorded in the animals of the control group, were attributed to delayed contact hypersensitivity. Under these experimental conditions and according to the maximization method of Magnusson and Kligman, the test item Bis LiTFMSI induces delayed contact hypersensitivity in 1/20 (5%) guinea pigs. However, the authors stated that LiTFMSI should not be considered as a skin sensitizer and should not be classified according to the EU criteria. Based on experimental data, LiTFMSI is not classified as sensitizing to skin according to the regulation called “classification, labelling and packaging” (CLP) of substances pursuant to European Commission 272/2008 criteria and to the Directive 67/548/EEC criteria (ECHA, 2023).

Repeated Dose Oral Toxicity Studies

Study 1: 28-day Rat Oral Repeated Dose Toxicity

Sixty Sprague-Dawley (SD IGS BR COBS-VAF®) rats were allocated to 4 groups and received LiTFMSI by oral route (gavage) administration once daily for 4 weeks, as follows:

Group 1 (10 M + 10 F): 0 mg/kg/day
Group 2 (5 M + 5 F): 1.67 mg/kg/day
Group 3 (5 M + 5 F): 10 mg/kg/day
Group 4 (10 M + 10 F): 60 mg/kg/day (ECHA, 2023)

Five male and five female rats from Group 1 (control rats) and Group 4 (high dose 60 mg/kg/day) stopped receiving LiTFMSI dosing on week 5 and were held for 2 weeks for a recovery study. The study was performed according to the OECD Guideline 407 (Repeated Dose 28-Day Oral Toxicity Study in Rodents). Rat age at study initiation: 28 ± 1 days old (four weeks old). The weight of rats at study initiation was reported as 70–83 g. No sex specific weights were reported; therefore, it was assumed that the range was for both male and female rats at the initiation of the study. The final weight of the rats was not reported other than there was normal weight gain and that there was no difference between the dose and control body weight at the end of the study.

Clinical Signs (see Table 3) **and Mortality Study 1**

All animals survived until scheduled sacrifice. No treatment-related changes in body weight development and food consumption were observed during the study.

Table 3: Clinical Signs Study 1

Sex	**Male**				**Female**			
Dose-level (mg/kg/day)	**0**	**1.67**	**10**	**60**	**0**	**1.67**	**10**	**60**
Number of animals/group	10	5	5	10	10	5	5	10
Piloerection	0	0	1	10	0	0	1	10
Abnormal gait	0	0	0	9	0	0	1	10
Fur loss	0	0	0	3	0	0	0	0
Body tremors	0	0	0	4	0	0	0	0
Lethargy	0	0	0	4	0	0	0	0
Hypersensitivity	0	0	0	10	0	0	1	10
Swollen right eye	1	0	0	0	0	0	0	0

Hypersensitivity, piloerection and abnormal gait (walking on toes) were seen intermittently among male and female rats treated with LiTFMSI at 60 mg/kg/day, mainly during the first half of the treatment period (see Table 2). Body tremors and lethargy were noted for four male rats at this dosage level on day 22. Slight fur loss was noted for three male rats treated at 60 mg/kg/day from day 4 to 15.

For rats treated at 10 mg/kg/day, piloerection was noted for one male rat on days 7 and 11 and for one female on days 11, 21 and 22. Piloerection was accompanied, for the female rats, on days 21 and 22 by hypersensitivity and abnormal gait. No clinical signs were seen for the remaining rats in this group throughout the treatment period. No clinical signs were seen during the treatment period amongst rats treated at 1.67 mg/kg/day or for control rats. No clinical signs were seen for control rats or rats previously treated at 60 mg/kg/day during the recovery period.

Body Weight Study 1
No significant differences in group mean body weight or cumulative body weight gain were recorded between treated and control rats of either sex during the treatment period. During the recovery period, females previously treated at 60 mg/kg/day showed a statistically significantly lower ($P < 0.05$) cumulative body weight gain relative to controls. However, group mean body weights for these rats were comparable to those of controls and the variation was considered by the authors to be coincidental. Group mean body weights and cumulative gains for male rats previously treated with LiTFMSI were similar to those of controls during the recovery period.

Food Consumption Study 1
For females receiving 60 mg/kg/day cumulative food consumption for the treatment period was statistically significantly higher ($P < 0.01$) relative to controls. However, the percentage increase was only 5% and the variation was not considered to be treatment related. Food consumption values for females during the recovery period and for males throughout the study were comparable to controls.

Clinical Chemistry Study 1
At Week 5: Statistically significantly ($P < 0.01$) higher albumin (A) and lower globulin (G) levels were recorded for male and female rats treated at 60 mg/kg/day (see Table 4). The A/G ratio was consequently increased for these animals, achieving statistical significance ($P < 0.01$) in comparison with controls. The total protein remained unaffected.

Table 4: Blood Chemistry Parameters (Week 5) Study 1

Sex	Male				Female			
Dose-level (mg/kg/day)	**0**	**1.67**	**10**	**60**	**0**	**1.67**	**10**	**60**
Glucose (mg/dL)	109	112	112	122*	122	114	121	117
Total protein (g/dL)	6.1	6.1	6.0	6.0	6.5	6.2	6.2	6.4
Albumin (g/dL)	2.7	2.8	2.8	3.1**	2.9	2.9	3.0	3.3**
Globulin (g/dL)	3.4	3.2	3.2	2.9**	3.5	3.2*	3.3*	3.1**
A/G ratio	0.78	0.87*	0.89*	1.05**	0.83	0.91*	0.92*	1.05**

Table 4: Blood Chemistry Parameters (Week 5) Study 1

Sex	Male				Female			
Dose-level (mg/kg/day)	**0**	**1.67**	**10**	**60**	**0**	**1.67**	**10**	**60**
Urea Nitra (mg/dL)	12	12	11	16**	11	14	12	14**
AP (mU/mL)	376	373	350	498**	209	270	290	268
K (mEq/L)	3.7	3.9	3.9	3.4	3.8	3.7	3.6	3.2**
Cl (mEq/L)	98	97	96*	97*	98	99	99	99
Cholesterol (mg/dL)	75	75	66	30**	73	61*	60*	59*
Tri-glyc (mg/dL)	114	106	104	66**	59	71	59	53

* Significantly lower than control rats ($p<0.05$).
** Significantly lower than control rats ($p<0.01$).

Lower globulin levels (achieving statistical significance for females, $P < 0.05$) were also seen for male and female rats treated at 10 and 1.67 mg/kg/day, with an associated higher A/G ratio. The change in A/G ratio achieved statistical significance ($P < 0.05$) for both sexes in comparison with controls. However, the magnitude of the difference from control was small and a strict dosage relationship was not observed. The authors concluded that a continuation of the possible effect seen on the high dosage was considered unlikely and statistically significant differences in globulin, and A/G ratios for rats dosed at 10 or 1.67 mg/kg/day were considered to be chance occurrences.

Cholesterol and triglyceride levels were lower than controls for male rats treated at 60 mg/kg/day, this change was statistically significant ($P < 0.01$). Significantly lower than control cholesterol levels ($P < 0.05$) were also recorded for female rats at all dosage levels. Although these differences were considered of minor importance, the possibility of a treatment relationship could not be excluded.

Blood urea nitrogen (BUN) levels were statistically significantly higher ($P < 0.01$) for male and female rats treated at 60 mg/kg/day than for controls. The magnitude of the difference in female rats was small and there was overlap of individual values between the groups. A treatment-related effect on BUN was not considered likely for female rats.

Statistically significantly higher alkaline phosphatase (AP) levels ($P < 0.01$) were recorded for male rats treated at 60 mg/kg/day in comparison with controls.

Slightly lower potassium ion concentration was recorded for female rats treated at 60 mg/kg/day, achieving statistical significance in comparison with controls ($P < 0.01$).

Chloride ion concentration was statistically significantly lower for male rats treated at 60 and 10 mg/kg/day than for controls ($P < 0.01$, $P < 0.05$ respectively). There was no dose relationship for Chloride ion concentration and the change was minor. This difference was considered to have arisen by chance.

Statistically significantly higher glucose levels ($P < 0.01$) were recorded for male rats treated at 60 mg/kg/day in comparison with controls. The individual values showed considerable variation and a treatment-related effect was not suspected.

Blood chemistry changes seen in week 5 were not seen at week 7 following the recovery period. Higher globulin levels (with consequently higher total protein levels) were recorded for female rats previously treated at 60 mg/kg/day, achieving statistical significance ($P < 0.01$). However, the authors stated that this was a minor change and was not thought to be related to treatment with LiTFMSI.

Urinalysis Study 1
At Week 5: Statistically significantly lower urinary pH ($P < 0.01$) was recorded for male and female rats treated at 60 and 10 mg/kg/day in comparison with controls.

The volume of urine collected was statistically significantly higher ($P < 0.05$) for male rats treated at 60 mg/kg/day than for controls. However, intergroup differences in urine volume were not strictly dosage-related and there was considerable variation in individual values and overlaps between the groups. This apparent change may have arisen by chance.

At Week 7: Slightly lower urinary pH was recorded for male and female rats previously treated with 60 mg/kg/day following the recovery period. This change achieved statistical significance ($P < 0.01$) in comparison with the controls.

There was no significant difference in the volume of urine collected between control and treated male rats.

Organ Weights Study 1
At Week 5: Increased liver weights (absolute and adjusted) were recorded for male and female rats treated at 60 mg/kg/day, achieving statistical significance ($P < 0.01$) in comparison with controls. Statistically significantly higher kidney (adjusted) weights ($P < 0.05$) were also recorded for male rats treated at 60 mg/kg/day in comparison with controls. Higher spleen weights were also recorded for male rats treated at 60 mg/kg/day, achieving statistical significance ($P < 0.05$) in comparison with controls. The authors stated that this apparent change was minor and was not dose-related. There was no histopathological finding in the spleen.

At Week 7: Higher absolute brain weights were recorded for male rats previously treated at 60 mg/kg/day. This difference was statistically significant ($P < 0.05$) when compared to controls. For female rats previously treated with LiTFMSI at 60 mg/kg/day, statistically significantly lower absolute spleen weights ($P < 0.05$) were recorded in comparison with controls.

Gross Pathology Study 1
At **Terminal kill** Enlarged livers were seen for all five male and three of the five female rats treated at 60 mg/kg/day. All other findings were considered to be incidental and not related to treatment. At **Recovery kill** an enlarged liver was seen for one male rat previously treated at 60 mg/kg/day following a 2-week recovery period. No other findings were considered to be related to treatment with LiTFMSI.

Histopathology Study 1
Histological examination was confined to the heart, spleen, kidneys and adrenals of terminal rats in Groups 1 and 4 only and the livers of all rats in the study. The following comments are made in summary. Liver: Generalized hepatocyte enlargement was recorded in all male rats and 4/5 female rats given 60 mg/kg/day LiTFMSI. A single female rat given 60 mg/kg/day LiTFMSI showed centrilobular hepatocyte enlargement. These changes were not recorded in any rats in any other treated group and there was no evidence of hepatocyte enlargement in rats given 60 mg/kg/day following a 2-week recovery period. All other changes seen were considered by the authors to be spontaneous in origin and therefore of no toxicological importance.

Macroscopic Pathology Study 1 (Terminal kill)
Enlarged livers were seen for all five male and 3/5 female rats treated at 60 mg/kg/day. In recovery group, an enlarged liver was seen for 1 male rat from the high dosage group.

Microscopic Pathology Study 1 (Terminal kill)
Generalized hepatocyte enlargement was seen in all male and 4/5 female rats treated at 60 mg/kg/day. The remaining female showed centrilobular hepatocyte enlargement.

Conclusions Study 1
In this subacute study with LiTFMSI, the liver was identified as a primary target organ at the high dosage of 60 mg/kg/day particularly in males. The livers were enlarged, increased in weight, and showed generalized hepatocyte enlargement. The thrombo-test times were also higher for male rats and since clotting factors are proteins, this could also be linked to a treatment-related effect in the liver. Higher blood urea nitrogen and alkaline phosphatase levels were recorded for male rats at 60 mg/kg/day in comparison with controls. Also, at 60 mg/kg/day clinical signs of toxicity were seen (e.g., piloerection, lethargy) increased kidney weights for males, and significantly decreased cholesterol and triglyceride levels, and a possible disturbance of urinary pH. No histopathological effect on the kidney was seen. Slightly lower potassium ion concentration was recorded for females treated at 60 mg/kg/day in comparison with controls. Following the 2-week recovery period for rats treated at 60 mg/kg/day, no effect on liver weight and hepatocyte enlargement was no longer apparent histopathologically.

At the dosage of 10 mg/kg/day, a slight increase in thrombo-test time in males was statistically significant and there was a minor decrease in plasma cholesterol level among females. Also, at 10 mg/kg/day there was a minor disturbance of urinary pH, but

no effect on kidney weight and no histopathological effect on the liver. At 10 mg/kg/day increased liver weight and histopathology (hepatocellular hypertrophy) was observed at termination. At 2-week recovery, the 60 mg/kg/day dose group had normal liver weight and histopathology. At 10 mg/kg/day, there were biochemistry effects as evidenced by higher albumin and lower globulin (with consequently higher A/G ratios) were recorded for male and female rats. Slightly lower cholesterol levels were observed for females at all dosages of LiTFMSI.

Conclusions of 28-day Rat Oral Repeated Dose Study 1
The 32-day oral gavage lowest-observed-adverse-effect-level (LOAEL) is 10 mg/kg/day based on liver weight and histopathology (hepatocyte enlargement), biochemistry (decreased cholesterol) and higher thrombo-test times. After 2-week recovery, liver weight and histopathology (hepatocyte enlargement) and thrombo-test times at 60 mg/kg/day were no different from controls. However, even with reversibility it is reasonable to conclude that liver effects (including higher thrombo-test time) at 10 mg/kg/day are an adverse effect (i.e., a LOAEL) and represent a continuation of the signs seen at 60 mg/kg/day. The authors stated that, “At the low dosage of 1.67 mg/kg/day there were no differences from controls considered to be of toxicological importance.” Other than for a possible minor reduction in plasma cholesterol level for females only, and “generalized hepatocyte enlargement” at terminal kill, but not after recovery for males, the 1.67 mg/kg/day LiTFMSI can be regarded as a no observed adverse effect level (NOAEL) for this 28-day oral (gavage) study in rats.

Study 2: 28-day Rat Oral Repeated Dose Toxicity
Groups of 10 male and female Sprague-Dawley rats were dosed with LiTFMSI at oral gavage doses of 0, 15, 45 and 90 mg/kg/day for 29 days (ECHA, 2023). At the end of the treatment period, the satellite animals (Groups 1 and 4) were kept for a 2-week treatment-free period. The control and high-dose rats (five rats of each sex) were allowed a 2-week treatment-free period to evaluate the reversibility of any findings. The first five (principal) surviving animals were killed at the end of the treatment period while the remaining animals (satellite) were kept for a 2-week treatment-free period. The test item was given as a solution in purified water under a constant dose-volume of 5 mL/kg. The animals were checked daily for mortality and clinical signs. Detailed clinical observation was conducted weekly and a functional observation battery was performed at the end of the treatment period. Body weight and food consumption were recorded once a week. Hematology, blood biochemical investigations were performed at the end of the treatment period. The hematology and blood chemistry investigations were repeated at the end of the treatment-free period (selected parameters) on all surviving satellite animals. Designated organs were weighted, and selected tissue specimens were preserved. A microscopic examination was performed on selected tissues from all animals and macroscopic lesions.

Mortality Study 2
No test-treatment related mortalities were observed during the study.

Clinical Signs Study 2
Round back was seen in animals given 45 and 90 mg/kg/day (1/5 males at each dose-level). Piloerection was especially noted for 3/5 males given 90 mg/kg/day. One test-treated male and female showed signs of ptyalism (hypersalivation) at 90 mg/kg/day (1/5 male and 1/5 female). Aggressive behavior, often associated with hypersensitivity to touch, was noted in females given 45 mg/kg/day and in both males (1/5 principal and 2/5 satellite animals) and females (1/5 principal and 1/5 satellite animals) given 90 mg/kg/day and were also noted during the treatment-free period. All these clinical signs were considered to be treatment related.

Detailed Clinical Observation and Functional Observation Battery Study 2
Both males and females given 90 mg/kg/day showed a slight to very slight increase in motor activity. The authors stated that the males of the high dose-level showed evidence of perturbation of autonomic or physiological functions described as "withdrawal following touch escape and absence of auditory startle reflex."

Body Weight Study 2
A moderately higher mean body weight gain, toxicologically significant, was noted in females given 90 mg/kg/day during the treatment period when compared to controls.

Food Consumption Study 2
In the 90 mg/kg/day dose-group, slightly higher mean food consumption, toxicologically significant, was noted in females during the treatment period and in both sexes during the treatment-free period, when compared to controls.

Hematology Study 2
No significant differences of toxicological importance were noted between treated and controls in the hematological parameters.

Blood Biochemistry Study 2
A toxicologically significant dose-related decrease in cholesterol and triglyceride levels were noted in the animals given 45 or 90 mg/kg/day. An increase in alkaline phosphatase and alanine aminotransferase activities was noted in the animals given 90 mg/kg/day. These changes, which showed reversibility, were considered to be treatment related.

Urinalysis Study 2
There were no significant treatment-related changes in any of the urinary parameters examined.

Organ Weights Study 2
Significantly higher liver weights were seen at the end of the treatment period for the animals given 45 and 90 mg/kg/day. No other relevant changes in organ weights were observed at the end of the treatment-free period.

Macroscopic pathology Study 2
At the end of the treatment period, significant enlargement of the liver was observed for the males given 45 mg/kg/day (with accentuated lobular pattern) and both sexes at 90 mg/kg/day, with several greyish/ whitish areas on the liver. These macroscopic findings were no longer present at the end of the treatment-free period.

Microscopic Pathology Study 2
Significant hepatocellular hypertrophy in the liver was seen in animals given 90 mg/kg/day and in four males given 45 mg/kg/day. Significant thyroid follicular cell hypertrophy and decreased diameter of the follicular lumen were observed mainly in females given 90 mg/kg/day: a morphological change indicative of thyroid hyperactivity. All changes were considered to be treatment related.

Conclusions 28-day Rat Oral Toxicity Study 2
Rats were dose orally with LiTFMSI at 0, 15, 45 and 90 mg/kg/day for 28 days. Under these experimental conditions, the Lowest Observed Adverse Effect Level (LOAEL) was established at 45 mg/kg/day based on hepatocellular hypertrophy in male rats and decreased cholesterol and triglycerides in male and female rats. The No Observed Adverse Effect Level (NOAEL) was 15 mg/kg/day.

Study 3: Reproductive / Developmental Oral Toxicity
In a one-generation reproductive/developmental study, three groups of ten male and ten female Sprague-Dawley rats received LiTFMSI, daily, by gavage, before mating, during mating and, for the females, throughout gestation until day 5 postpartum (pp), at dose-levels of 15, 30 or 60 mg/kg/day for at least 4 weeks in males and up to 6 weeks in females (ECHA, 2023). ECHA determined this study was given a reliability score of 1 (“reliable without restriction”).

Methods Reproductive/Developmental Study 3
The materials and methods were reported as compliance with OECD Guideline 421 (Reproduction / Developmental Toxicity Screening Test) with no deviations and compliance with good laboratory practices (GLP). The test animal species used in this study were rats: male/female Sprague-Dawley (RjHan: SD; Rats CD®). Eighty-two rats (41 males and 41 females) were received at CiToxLAB France on 03 June 2014. Age/Weight: At the beginning of the treatment period, the males were 10 weeks old and had a mean body weight of 454 g (range: 406 g to 475 g). The females were 9 weeks old and had a mean body weight of 213 g (range: 196 g to 242 g). The animals were sexually mature and were not siblings. The females were virgin. The route of administration was oral gavage. The vehicle was water. LiTFMSI was not detected in control samples.

The dosing volume was 5 mL/kg/day. The LiTFMSI concentrations in the administered dosage forms were within acceptable range of variations (± 10% of the nominal concentrations). Animals were checked daily for clinical signs, mortality, and detailed clinical observations were conducted weekly. Body weights and food consumption were

recorded weekly until mating and then at designated intervals throughout gestation and lactation.

The animals were paired for mating after 2 weeks of treatment and the dams were allowed to litter and rear their progeny until day 5 pp. The total litter sizes and numbers of pups of each sex were recorded after birth. The pups were observed daily for clinical signs of toxicity and pup body weights were recorded on days 1 and 5 pp.

The males were sacrificed after completion of the mating period. Dams were sacrificed on day 5 pp. Body weights and selected organs weights were recorded, and a complete macroscopic post-mortem examination performed, with particular attention paid to the reproductive organs. A microscopic examination was also conducted on selected organs from the animals in the control groups and the high-dose groups. Microscopic examination was conducted on all macroscopic lesions from all groups.

Pups, including those found dead before study termination, were also submitted for a macroscopic post-mortem examination.

Duration of Treatment/exposure Reproductive/Developmental Study 3

In the males:
- 2 weeks before mating,
- during the mating period (up to 2 weeks),
- until sacrifice (at least 4 weeks in total).

In the females:
- 2 weeks before mating,
- during the mating period (up to 2 weeks),
- during gestation,
- during lactation until day 4 pp inclusive,
- until sacrifice for females with no evidence of mating or no delivery.

Doses / Concentrations:
0, 15, 30 and 60 mg/kg/day
Basis: actual ingested
No. of animals per sex per dose: 10
Control animals: yes, concurrent no treatment

Mortality (Parental Animals) Reproductive/Developmental Study 3

In control males and males at 15 mg/kg/day there were no unscheduled deaths. At 30 mg/kg/day one male was found dead on day 27 without any clinical signs prior to death. At macroscopic post-mortem examination, the ventricles of the heart, the liver and the kidneys were enlarged. Ureters showed translucent or brown content and were dilated. Dilated pelvis was noted in one kidney whereas black discoloration was seen in the other one.

At 60 mg/kg/day one male was sacrificed prematurely on day 2. Prior to sacrifice, signs of poor clinical condition were observed (ptyalism, half-closed eyes, round back, tremors, clonic contraction, convulsions, hypoactivity, prostration, decrease in grasping

reflex, locomotory difficulties and lateral decubitus). At macroscopic post-mortem examination, the prostate was gelatinous in consistency and the urinary bladder was dilated. Enlarged kidneys along with dilated ureters and dilated pelvis confirmed at microscopic evaluation were observed.

There were no unscheduled deaths in control females and females at 15 mg/kg/day. At 30 mg/kg/day one female was sacrificed for no delivery. This female was not pregnant. Three females were sacrificed for dead litter. Prior to sacrifice, piloerection was observed in one female sacrificed for dead litter. No necropsy findings were observed during macroscopic post-mortem examinations.

At 60 mg/kg/day two females were sacrificed for no delivery. These females were not pregnant. Two females were sacrificed for humane reasons (moribund) and one female was found dead. Five females were sacrificed for dead litter.

Clinical Signs (Parental Animals) Reproductive/Developmental Study 3
At 60 mg/kg/day, marked to severe clinical signs were observed both in males and females. Mostly neurological disorders were observed (i.e., tremors, clonic contraction, convulsions, tonic contraction, hypoactivity, prostration, decrease in grasping reflex, locomotory difficulties and/or hypersensitivity to the touch).

At 30 mg/kg/day, marked clinical signs were observed in one male on study day 26 and were consistent with the neurological disorders described at the high dose-level (i.e., tremors, convulsions, and tonic contraction). At 15 mg/kg/day, there were no treatment-related clinical findings.

Body Weight (Parental Animals) Reproductive/Developmental Study 3
MALES: At 15 or 30 mg/kg/day, and when compared with controls, there were no body weight effects. At 60 mg/kg/day, and when compared with controls, there was a minimal lower mean body weight on day 8 (-4.6%, $p < 0.01$) resulting in a lower mean body weight gain over the first week of treatment (+24 g vs. +38 g, $p < 0.05$).

FEMALES: During pre-mating and gestation periods there were no body weight effects. Lactation period: When compared with controls, there were dose-related decreases in mean body weight and mean body weight change at 15 and 30 mg/kg/day. The difference was only statistically significant for mean body weight change at 15 mg/kg/day (+16 g vs. +26 g in controls, $p < 0.05$). The absence of statistically significant differences at the high dose-level was considered by the authors to be due to large variation between the females.

Food Consumption (Parental Animals) Reproductive/Developmental Study 3
In males dosed at 15 mg/kg/day, when compared with controls, there were minimal reductions in mean food consumption during the first week of the treatment period (down to 32 g/animal/day at 60 mg/kg/day vs. 36 g/animal/day). Thereafter, mean food consumption returned towards control values. In females during pre-mating and gestation periods there were no effects.

During lactation period at 15 mg/kg/day, when compared with controls, there was a lower mean food consumption (down to 35 g/animal/day at 30 mg/kg/day vs. 48 g/animal/day, respectively, $p < 0.01$).

Reproductive Performance (Parental Animals) Reproductive/Developmental Study 3
A significantly higher mean pre-coital time (mean number of days taken to mate) was observed in females given 60 mg/kg/day, in particular due to one female which mated after 13 days (the female was blocked in diestrus for several days).

Lower fertility and gestation indexes were noted in females given 60 mg/kg/day. All females were pregnant, except one and two females at 30 and 60 mg/kg/day, respectively. The authors stated that at 60 mg/kg/day, the lower fertility and gestation indexes were considered to be related to the treatment with the test item.

Delivery data: In dose groups 15, 30 and 60 mg/kg/day, and when compared with controls, there was a dose-related decrease in viability index on day 4 pp (79.6%, 47.5% and 0.0% vs. 95.7%, respectively). At 60 mg/kg/day, when compared with controls, there was a high incidence of post-implantation loss (30.1% vs. 11.9% respectively). A few females delivered with all pups found dead during the period of days 1-4 pp.
Pup mortality: There were dose-related increased percentages of dead and cannibalized pups from 15 mg/kg/day.
Pup clinical signs: When compared with controls, there was a dose-related increased number of litters with pups with absence of milk in the stomach from 15 mg/kg/day.
Pup body weight and body weight gain: On days 1 and 5 pp, and when compared with controls, there were lower mean body weights and mean body weight changes from 15 mg/kg/day and higher.
Pups necropsy: In heart and cardiovascular examinations of the pups, there were no findings.

Organ Weights (Parental Animals) Reproductive/Developmental Study 3
No changes that could be related to treatment were noted in testis and epididymis weights.

Gross Pathology (Parental Animals) Reproductive/Developmental Study 3
All the necropsy findings observed in unscheduled deaths or at terminal sacrifice were recognized as those that are commonly noted in the rats of this strain and age. None of the findings were considered to be treatment related.

Histopathology (Parental Animals) Reproductive/Developmental Study 3
No microscopic changes that could be related to treatment were noted in the examined organs of males and females from Group 4 (60 mg/kg). Increased incidence and severity of follicle development was seen in the ovaries from unscheduled dead or surviving females in Group 4. In 2/10 females, ovocytes were noted in the lumen of oviducts indicating that estrus just occurred. Recent basophilic corpora lutea were also

observed in 3 of these females. All these changes are related to the estrus cycle and suggested that females from Group 4 were possibly at a different stage than controls. An evaluation of these females to determine a more precise cycle stage was impossible in the absence of uterus and vagina examination. A relationship to treatment of this slight change in Group 4 remained unclear.

The effect level was less than 15 mg/kg/day (actual dose received) based on effect on body weight at this dose-level and, mortality and clinical signs from 30 mg/kg/day. The authors stated that reproductive performance and embryo/fetal development NOAEL was identified at 30 mg/kg bw/day (actual dose received) based on lower fertility and gestation indexes at 60 mg/kg/day.

Viability (F1 Offspring) Reproductive/Developmental Study 3
At 15, 30 and 60 mg/kg/day, when compared with controls, there was a dose-related decrease in viability index on day 4 pp (79.6%, 47.5% and 0.0% vs. 95.7%, respectively). The decreases in viability indexes were the consequence of increased incidences of dead and cannibalized pups on days 1 and 2 pp.

At 60 mg/kg/day, and when compared with controls, there was a high incidence of post-implantation loss (30.1% vs. 11.9 respectively). A few females delivered with all pups found dead during the period of days 1-4 pp.

The mean number of pups per litter (14.1, 15.2 and 13.3 for the control, low-dose, mid-dose groups, respectively) was comparable in all groups. The number of male and female litter mates was comparable in all groups. No effects were observed on the live born index or on the number of stillborn pups.

Mortality (F1 Offspring) Reproductive/Developmental Study 3
There were dose-related increased percentages of dead and cannibalized pups from 15 mg/kg/day. Dead and cannibalized pups were observed mostly on days 1 and 2 pp. These findings were considered to be treatment-related and observed in a context of severe to excessive maternal toxicity.

Clinical Signs (F1 Offspring) Reproductive/Developmental Study 3
When compared with controls, there were a dose-related increased numbers of litters with pups with absence of milk in the stomach from 15 mg/kg/day.

Body Weight (F1 Offspring) Reproductive/Developmental Study 3
When compared with controls, on days 1 and 5 pp, there were lower mean body weights and mean body weight changes from 15 mg/kg/day.

Gross Pathology (F1 Offspring) Reproductive/Developmental Study 3
In dead pups (non-autolyzed ones), there was absence of milk in the stomach. In surviving pups, there were no treatment-related findings at necropsy and in particular no findings observed in heart and cardiovascular examinations.

Reproductive Findings Study 3
After 2 or 27 days of treatment at 60 or 30 mg/kg/day respectively, excessive toxicity resulted in a panel of clinical signs, premature euthanasia and/or deaths, both in males and/or females. In terms of body weight and food consumption, males were mostly affected at 60 mg/kg/day while toxicologically significant reductions were observed in females from 15 mg/kg/day (mainly during the lactation period).

In this context of marked to severe parental toxicity, there were no effects on mating/fertility data up to 30 mg/kg/day (lower fertility and gestation indexes at 60 mg/kg/day), no effects on pregnancy parameter up to 30 mg/kg/day (increased post-implantation at 60 mg/kg/day) and decreased pup viability from 15 mg/kg/day.

The decreases in viability indexes were the consequence of increased incidences of dead and cannibalized pups on days 1 and 2 pp. At necropsy, dead pups (non-autolyzed ones) had no milk in the stomach. In this study, the marked to severe toxicity may have dramatically modified the maternal behavior leading to decreased pup viability at 15 mg/kg/day. Despite a context of severe to excessive maternal toxicity, there was no indication of any teratogenic potential (no test item treatment-related findings at necropsy of dead or surviving pups).

Developmental Findings Study 3
Pup mortality: There were dose-related increased percentages of found dead and cannibalized pups from 15 mg/kg/day.
Pup clinical signs: When compared with controls, there was a dose-related increased number of litters with pups with absence of milk in the stomach from 15 mg/kg/day.
Pup body weight and body weight gain: On days 1 and 5 pp when compared with controls, there were lower mean body weights and mean body weight changes from 15 mg/kg/day.
Pups necropsy: Heart and cardiovascular examinations of the pups showed no effects.
Pathology: There were no organs weight changes and macroscopic or microscopic findings considered to be treatment related.

Summary of Developmental/Reproductive Study 3
Rats were dosed orally with LiTFMSI at 0, 15, 30 and 60 mg/kg/day for 28 days. Based on the experimental conditions of this study:

- The NOAEL for parental (male and female) toxicity was lower than 15 mg/kg/day based on effect on body weight at this dose-level and, mortality and clinical signs from 30 mg/kg/day.
- The NOAEL for reproductive performance and embryo/fetal development was 30 mg/kg/day based on lower fertility and gestation indexes at 60 mg/kg/day.
- The NOAEL for toxic effects on progeny was lower than 15 mg/kg/day based on lower pup survival (viability) index on day 4 pp.
- A LOAEL was identified as 15 mg/kg/day based on decreased pup survival at day 4 postpartum (including pups killed by mother) and the absence of milk in pup stomachs.

Discussion
No inhalation studies for LiTFMSI were identified. The potential of portal-of-entry effects of LiTFMSI in the respiratory tract is not known. LiTFMSI is not a skin sensitizer; however, it is corrosive to the skin (ECHA, 2023).

LiTFMSI has a negligible vapor pressure of 0.27 mmHg at 25°C. With a melting point of 238°C it would be expected to be a solid at room temperature. However, LiTFMSI has a high-water solubility reported as 1730 g/L at 20°C (ECHA, 2023). LiTFMSI would be expected to be emitted to the air in an aqueous mixture and or readily dissolved in atmospheric moisture and the lung. Except for the possibility of some LiTFMSI being scrubbed out in the nose, 100% of LiTFMSI is assumed to be deposited in the thoracic (tracheobronchial and pulmonary) region of the respiratory tract. Because of LiTFMSI's high water solubility and stability (both hydrolytically and biologically), route-to-route (oral-to-inhalation) extrapolation is appropriate. The LiTFMSI that is deposited in the pulmonary region may be assumed to be absorbed to 100% and that remote site toxicity is of interest. The oral (gavage) toxicity studies summarized above provide reliable toxicological results and were used to derive candidate Reference Doses (RfDs).

Derivation of Initial Threshold Screening Levels
The two 28-day oral dose (gavage) studies that were performed in Sprague-Dawley rats showed that the effects in the liver are the most sensitive endpoints. Study 1 identified a slightly a lower LOAEL at 10 mg/kg/day compared to 45 mg/kg/day in Study 2 (see Table 5). The reproductive/developmental study identified a LOAEL at 15 mg/kg/day based on decreased pup survival; however, the authors of this study suggested that the "marked to severe toxicity may have dramatically modified the maternal behavior" at this dose level.

Table 5. Summary of Effect Levels for LiTFMSI in Oral (Gavage) Rat Studies

	28-day Study 1	**28-day Study 2**	**Reproductive/ Developmental Study 3**
LOAEL	10 mg/kg/day (liver weight and hepato-cellular hypertrophy, decreased cholesterol, and higher thrombo-test times)	45 mg/kg/day (hepatocellular hypertrophy and decreased cholesterol and triglycerides)	15 mg/kg/day (lower pup survival at day 4 postpartum and decreased milk in pup stomachs)
NOAEL	1.67 mg/kg/day	15 mg/kg/day	Not identified

Derivation of Chronic ITSL:
Candidate RfDs can be derived from the toxicological data described above. The data was not amenable to benchmark dose modeling because averages and standard deviations were not reported for liver weights in each dose group. Likewise, Study 1 did not report standard deviation for blood chemistry. The NOAEL in Study 2 (15 mg/kg/day) was higher than the LOAEL (10 mg/kg/day) from Study 1; therefore, using the NOAEL in Study 2 as a point of departure (POD) would not be protective for

potential liver effects. The NOAEL from Study 1 was used as the POD to derive a chronic RfD.

To calculate an RfD the animal and human body weights are used to estimate dose equivalency between animals and humans (i.e., Human Equivalent Dose or HED). At the beginning of Study 1, the body weights of the rats (male and female grouped) were reported as ranging from 70-83 g. The weights of the animals at eight weeks (at study termination) were not given in the study results; therefore, the terminal body weights must be estimated. The weight of the males and female Sprague-Dawley rats can be determined from the CD® (Sprague Dawley) IGS Rat (Crl:CD(SD) Outbred) growth curves as found online at Charles River Labs (criver.com). The approximate weights for male and female rats at 8 weeks are 275 g and 200 g, respectively (see Appendix, Figure 1). The default body weight of humans is assumed to be 70 kg (EPA, 2011).

The NOAEL animal dose was converted to a HED species-specific, dosimetric adjustment factor (DAF) addressing predominately toxicokinetic and some toxicodynamic aspects of the interspecies uncertainty factor, UF_A (EPA, 2011). The derivation of the DAF is:

$$DAF = (BW_a / BW_h)^{1/4}$$

Where BW is the body weight, and the subscripts “a” indicates animal and “h” indicates human. The HED is calculated as:

$$HED = \text{animal dose} \times DAF$$

For female rats: $HED = 1.67 \text{ mg/kg-day} \times (0.200 \text{ kg}/70 \text{ kg})^{0.25} = 1.67 \times 0.231 = 0.385 \text{ mg/kg}$

For male rats: $HED = 1.67 \text{ mg/kg-day} \times (0.275 \text{ kg}/70 \text{ kg})^{0.25} = 1.67 \times 0.250 = 0.418 \text{ mg/kg}$

The HED for the female rat was selected as the point of departure since using the male rat HED would not be protective for female rats.

The chronic RfD can be calculated as follows:

$$RfD = (POD)/(UF1 \times UF2 \times UF3 \times UF4)$$

Where POD is the Point of Departure
UF1 is an Uncertainty Factor (UF) of 10 for intraspecies extrapolation
UF2 is 3 for interspecies extrapolation (when body weight scaling is used)
UF3 is 3 for subacute to subchronic duration
UF4 is 10 for subchronic to chronic duration

$$RfD = (0.385 \text{ mg/kg})/(3 \times 10 \times 3 \times 10)$$
$$RfD = 0.000385 \text{ mg/kg}$$

An Initial Threshold Screening Level (ITSL) is derived from the RfD pursuant to Rule 232(1)(b) as follows:

ITSL = RfD x 70 kg/20 m^3 × unit conversion
ITSL = (0.000427 mg/kg) 3.5 × 1000 µg/mg
ITSL = 1.35 µg/m^3 ; rounded to 1 significant figure is 1 µg/m^3 with annual averaging time.

Alternative Calculation for Chronic ITSL

As specified in Rule 232(1)(e) an ITSL can be calculated as shown below:

ITSL = NOAEL(mg/kg/day)/(35 × 100) × Wa/Ia × b/a × unit conversion

Where Wa is the weight of the animal = 0.2 kg
Ia is the inhalation rate of the animal
b = Absorption efficiency by the oral route of exposure.
a = Absorption efficiency by the inhalation route of exposure.

Since the ratio of b/a is unknown, this value defaults to 1. Note that the equation for 232(1)(e) is used to extrapolate a 7-day study to a chronic health benchmark. Because the oral gavage study (Study 1) was a 28-day study the uncertainty factor of 35 is decreased to 20 to account for the increased duration of exposure and less uncertainty when extrapolating to the chronic exposure scenario.

The daily inhalation rate for male and female rats is determined by the algorithm in the Table below (EPA, 1988):

TABLE 4-2

Allometric Relationships for Inhalation Rate in m^3/day (I) to Body Weight in kg (W)

Animal Group	Allometric Equation	r^2	Figure
All species combined	$I = 0.66\ W^{0.7579}$	0.96	4-3
Monkeys	$I = 0.81\ W^{0.4862}$	0.72	4-5
Guinea pigs	$I = 0.44\ W^{0.5156}$	0.32	4-8
Hamsters	$I = 0.50\ W^{0.9017}$	0.86	4-9
Mice	$I = 1.99\ W^{1.0496}$	0.87	4-10
Rats	$I = 0.80\ W^{0.8206}$	0.77	4-11
Cats	$I = 0.32\ W^{0.5945}$	0.81	4-12
Dogs	$I = 0.67\ W^{0.7091}$	0.89	4-13
Rabbits	$I = 0.46\ W^{0.8307}$	0.88	4-14

From EPA (1988)

The inhalation rate is a function of the body weight:

$I = 0.8 \times W^{0.8206}$

Male rat daily inhalation rate using a body weight (W) of 0.275 kg:

$I_{MR} = 0.8 \times 0.275^{0.8206} = 0.277$ m³/day

Female rate daily inhalation rate

$I_{FR} = 0.8 \times 0.2^{0.8206} = 0.214$ m³/day

The ratio of Wa/Ia for the male rat is 0.275/0.277 = 0.992 kg/m³/day.
The ratio of Wa/Ia for the female rat is 0.2/0.214 = 0.937 kg/m³/day.

A candidate ITSL can be developed from the NOAEL of 1.67 mg/kg/day from Study 1 using Rule 232(1)(e) as follows:

ITSL = (1.67 mg/kg/day)/(20 × 100) × 0.2 kg/(0.214 m³/day) × 1000 µg/mg
ITSL = 0.78 µg/m³
ITSL = 0.8 µg/m³; rounded to 1 significant figure

Note that the female rat body weight and inhalation rate were used because if the male rat body weight and inhalation rate were used the resulting ITSL would not be protective for female rats. Additionally, this screening level of 0.8 µg/m³ (annual avg. time) was not used as the final chronic ITSL because EPA's (2011) body weight scaling to the ¾ power is a more accurate method of extrapolating animal dose to human equivalency.

Derivation of the Acute ITSL Based on Reproductive/Developmental Toxicity
An ITSL can be developed from a Reference Dose (RfD) pursuant to Rule 232(1)(b). The reproductive LOAEL of 15 mg/kg/day was used to derive an RfD. The LOAEL from Study 3 of 15 mg/kg/day was used as the Point of Departure (POD). The body weight of the maternal rat was used to calculate the Human Equivalent Dose (HED). As described above, the HED is calculated as HED = POD × DAF, and the DAF is calculated based on EPA (2011) as DAF = $(BW_{animal}/BW_{human})^{¼}$.

As stated in the methodology of Study 3, the 10-week-old female Sprague-Dawley RjHan: SD (Rats CD®) had an average initial body weight of 213 g (n=40). By the end of the study the body weight gain of the low dose female rat group was reported as +16 g. Therefore, it is reasonable to estimate the final body weight of the Sprague-Dawley, RjHan: SD (Rats CD®) at the 15 mg/kg dose level as 213 g + 16 g = 229 g. The HED is calculated as:

HED = POD × DAF
HED = POD from the animal study × $(BW_{animal} / BW_{human})^{¼}$
HED = 15 mg/kg × $(0.229 \text{ kg}/70 \text{ kg})^{¼}$
HED = 15 mg/kg × 0.239
HED = 3.587 mg/kg

Using the HED as the POD, the RfD is calculated as:

RfD = POD/(UF1 x UF2 x UF3)

Where

UF1 = 10 for sensitive subpopulations (i.e., intraspecies)
UF2 = 3 for animal to human extrapolation (i.e., interspecies)
UF3 = 10 for LOAEL to NOAEL extrapolation

Note that the UF2 for interspecies extrapolation is reduced from 10 to 3 when interspecies scaling is used (EPA, 2011).

$RfD = POD_{HED}/(UF1 \times UF2 \times UF3) \times$ unit conversion
RfD = (3.587 mg/kg)/(10 × 3 × 10) × 1000 µg/mg
RfD = 11.96 µg/kg

The ITSL is calculated from the RfD pursuant to Rule 232(1)(b) as follows:

ITSL = RfD x 70 kg/20 m^3
ITSL = 11.96 µg/kg × 3.5 kg/m^3
ITSL = 41.85 µg/m^3
ITSL = 40 µg/m^3; rounded to 1 significant figure

The averaging time for the acute ITSL is 24-hrs. to account for the short exposure duration in which reproductive effects could occur.

Summary and Conclusion

Candidate chronic ITSLs were derived from subacute oral gavage study using two methods and resulted in nearly identical results:

RfD methodology based ITSL = 1 µg/m^3
Rule 232(1)(e) based ITSL = 0.8 µg/m^3

The RfD-based methodology was deemed more appropriate because using the body weight scaling of $(BW_{animal}/BW_{human})^{1/4}$ provides a human equivalent dose which is better at addressing toxicokinetic and some toxicodynamic aspects of interspecies extrapolation. Therefore, the RfD methodology resulting in the ITSL of 1 µg/m^3 (annual averaging time) was selected to be protective of chronic exposure to LiTFMSI.

To protect for acute exposures during reproduction and development, the acute ITSL is 40 µg/m^3 with 24-hr averaging time.

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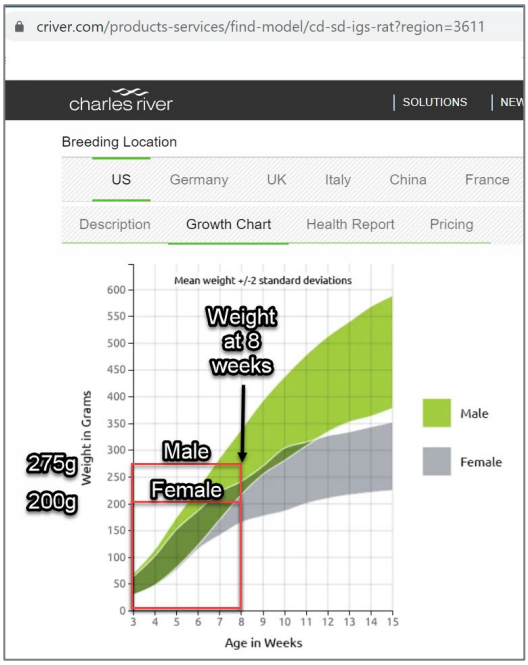
Appendix

Figure 1. Sprague-Dawley Rat Growth Curves Used to Estimate Male and Female Body Weights



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