講演資料３

ラットを用いたアルミニウム塩の二世代生殖毒性試験

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Two-Generation Reproductive Toxicity Study of Aluminium Salts in Rats

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これまでの研究: 雄の生殖への影響（強制経口投与）

反復強制経口投与試験において、雄の生殖毒性が観察されている。

- 塩化アルミニウムのラット6ヶ月試験において、精子/精巣毒性が2.5 mg Al/kg/dayで認められた（Krasovskii et al, 1979）。
- NZWウサギの16週試験（6.9 mg Al/kg/dayの塩化アルミニウムを隔日投与）において、性欲障害、精子毒性が観察された（Yousef et al, 2005）。
- 硫酸アルミニウムのラット21日試験において、精原細胞の減少が86及び172 mg Al/kg/dayでみられた（Roy et al, 1991）。

- これらの経口投与試験では、飼料中のアルミニウム含量は測定されていない。
- 強制経口投与による一時の大量投与後のトキシコキネティクスは、ヒトでの食物を介した持続的な摂取とは異なると思われるので、ヒトのリスクアセスメントにおけるこれらの動物試験の妥当性には疑問が残る。

Previous study: Male Reproductive Effects (Oral Gavage Study)

Male reproductive toxicity was observed in repeated oral (gavage) dose studies.

- In a 6-month study of aluminium chloride in rats, sperm/testicular toxicity was observed at 2.5 mg Al/kg/day (Krasovskii et al, 1979).
- In a 16-week study of aluminium chloride (6.9 mg Al/kg, every other day) in NZW rabbits, sperm toxicity and decreased libido were found (Yousef et al, 2005).
- In a 21-day study of aluminium sulfate in rats, spermatogonial cells were decreased at 86 and 172 mg Al/kg/day (Roy et al, 1991).

- In these oral gavage studies, aluminium content in the diet was not determined.
- The relevance of these oral gavage studies for human risk assessment is unclear because the toxicokinetics after a bolus dose by gavage must differ significantly from those after actual continuous exposure via the diet in humans.

これまでの研究: 雄の生殖への影響（混餌投与）

- 飼料中のアルミ含有量を考慮した試験
  - 塩基性リン酸アルミニウムナトリウム（SALP）または水酸化アルミニウムのラット28日試験では、302 mg Al/kg/dayまで精巣の病理組織学的検査で影響はみられなかった（Hick et al, 1987）。
  - 塩基性SALPのビーグル犬の26週試験では、75 mg Al/kg/dayで精巣毒性が認められた（Pettersen et al, 1990）。
  - 酸性SALPのビーグル犬の26週試験では、88 mg Al/kg/dayまで精巣毒性はみられなかった（Katz et al, 1984）。

- これらの研究では、消化管吸収率が低いと考えられる不溶性/難溶性のアルミニウム化合物が用いられている。

Previous study: Male Reproductive Effects (Dietary Study)

- Continuous exposure studies, taking into account the aluminium content in the basal diet:
  - In a 28-day dietary exposure study of basic sodium aluminium phosphate (SALP) or aluminium hydroxide in rats, no changes in the testicular histopathology were observed up to 302 mg Al/kg/day (Hicks et al, 1987).
  - In a 26-week feeding study of SALP basic in beagle dogs, testicular toxicity was found at 75 mg Al/kg bw/day (Pettersen et al, 1990).
  - In a 26-week feeding study of SALP acidic in beagle dogs, testicular toxicity was not detected up to 88 mg Al/kg/day (Katz et al, 1984).

- These dietary studies used water-insoluble or sparingly-soluble forms of aluminium, which are widely assumed to be less bioavailable than soluble compounds.

これまでの研究: 雌の生殖への影響

- 硝酸アルミニウムの生殖/発生毒性試験

  [ラットの雄には交配前60日間、雌には交配前14日から交配、妊娠及び授乳期間を通して180, 360, 720 mg/kg bw/day (硝酸アルミニウムの量か水和物の量か不明)を**強制経口投与**]:

  最高用量群で黄体数減少、リッター数減少、360 mg/kg bw以上の投与群で生存同腹児数減少、すべての投与群で児体重低下が観察された（Domingo et al. 1987）。

- 母動物へストレスとアルミニウム暴露の複合影響を調べた試験

  [SDラットの雌に硝酸アルミニウム(50, 100 mg Al/kg bw/day)及びクエン酸を15日間**飲水投与**し、未投与雄ラットと交配。妊娠及び授乳期間中にも投与を持続 (飼料中アルミニウム濃度: 42 ug Al/kg)]

  妊娠期間、同腹児数や出生時体重に変化なし（Colomina et al. 2005）。

Previous study: Female Reproductive Effects

- In a reproductive/developmental toxicity study of aluminium nitrate in SD rats [oral gavage administration, beginning 60 days (males) or 14 days (females) before mating throughout the mating, gestation and lactation periods], there were decreases in the number of litters and corpora lutea at 720 mg/kg/day, the number of living pups at 360 mg/kg/day and above, and body weights of pups at 180 mg/kg/day and above (unclear if dose is expressed as aluminium or aluminium nitrate) (Domingo et al. 1987)

- In a study to assess the potential combined influence of maternal stress and aluminium exposure on postnatal development and behavior of the offspring [female SD rats, administered 50 or 100 mg Al/kg/day aluminium nitrate in drinking water with citric acid, beginning 15 days before mating through the gestation and lactation periods, basal diet contained 42 ug Al/kg] , no changes were found in the gestation period, litter size and birth weight (Colomina et al. 2005).

これまでの研究：発生毒性（強制経口投与）

化合物	動物	投与期間	最少毒性量と主な毒性	文献
硝酸アルミニウム	ラット	妊娠 6–14日	22.8 mg Al/kg bw/day* ↓胎児体重、尾長、↑骨格奇形/変異	Paternain et al. 1988
水酸化アルミニウム	ラット	妊娠 6–10日	266 mg Al/kg bw/dayまで 発生影響なし	Gomez et al. 1990
水酸化アルミニウム	マウス	妊娠 6–15日	92 mg Al/kg bw/dayまで 発生影響なし	Domingo et al. 1989; Colomina et al. 1992
乳酸アルミニウム	マウス	妊娠 6–15日	57.5 mg Al/kg bw/day* ↓胎児体重、↑口蓋裂・骨化遅延	Colomina et al. 1992
水酸化アルミニウム	マウス	妊娠8, 9, 10, 11または12日	72 mg Al/kg bw/day* ↓胎児体重・骨化遅延	Albina et al. 2000
硝酸アルミニウム	ラット	妊娠14日 –出産後21日	13 mg Al/kg bw/day** ↓児体重・尾長	Domingo et al., 1987c
乳酸アルミニウム	ラット	生後 5–14日	200 mg Al/kg bw/day ↑児死亡率、↓児体重増加	Bernuzzi et al., 1989b

*母体毒性量
**母体毒性に関する情報なし

Previous study: Developmental Effects

Oral gavage study

Compounds	Animals	Exposure period	LOAEL & Major toxic effects	Reference
Aluminium nitrate	Rats	GD6-14	22.8 mg Al/kg bw/day* Body weight and tail length of fetuses↓, skeletal malformations/variations	Paternain et al. 1988
Aluminium hydroxide	Rats	GD6–10	No effects on development up to 266 mg Al/kg bw/day	Gomez et al. 1990
Aluminium hydroxide	Mice	GD6-15	No effects on development up to 92 mg Al/kg bw/day	Domingo et al. 1989; Colomina et al. 1992
Aluminium lactate	Mice	GD6-15	57.5 mg Al/kg bw/day* Fetal body weight↓, cleft plate, dorsal hyperkyphosis, delayed ossification	Colomina et al. 1992
Aluminium hydroxide	Mice	GD8, 9, 10, 11 or 12	72 mg Al/kg bw/day* Fetal body weight↓, delayed ossification	Albina et al. 2000
Aluminium nitrate	Rats	GD14-LD21	13 mg Al/kg bw/day** Body weight and tail length of pups↓	Domingo et al., 1987c
Aluminium lactate	Rats	PND5-14	200 mg Al/kg bw/day Mortality↑, body weight gain ↓	Bernuzzi et al., 1989b

GD: gestational day, LD: lactation day, PND: postnatal day
*with maternal toxicity, **no data available on maternal toxicity

これまでの研究：発生毒性（混餌投与）

化合物	動物	投与期間	最小毒性量と主な毒性	文献
塩化アルミニウム	ラット	妊娠8日−分娩	155 mg Al/kg bw/day ↑児生後死亡率、↓児体重	Bernuzzi et al., 1986
塩化アルミニウム	ラット	妊娠1日−分娩	273 mg Al/kg bw/day* ↑児生後死亡率、↓児体重	Bernuzzi et al., 1989a
乳酸アルミニウム	ラット	妊娠1日−分娩	378 mg Al/kg bw/day* ↑児生後死亡率、↓児体重	Bernuzzi et al., 1989a
乳酸アルミニウム	ラット	妊娠1−7日、妊娠1−14日または妊娠1日−分娩	400 mg Al/kg bw/dayまで 児生存率や体重に影響なし	Muller et al., 1990

*母体毒性量

- これらの研究では、飼料中のアルミニウム含量は測定されていない。

Previous study: Developmental Effects

Feeding study

Compounds	Animals	Exposure period	LOAEL & Major toxic effects	Reference
Aluminium chloride	Rats	GD8-delivery	155 mg Al/kg bw/day Postnatal mortality↑, body weight of pups↓	Bernuzzi et al., 1986
Aluminium chloride	Rats	GD1-delivery	273 mg Al/kg bw/day* Postnatal mortality↑, body weight of pups↓	Bernuzzi et al., 1989a
Aluminium lactate	Rats	GD1-delivery	378 mg Al/kg bw/day* Postnatal mortality↑, body weight of pups↓	Bernuzzi et al., 1989a
Aluminium lactate	Rats	GD1-7, GD1-14 or GD1-delivery	No effects on postnatal mortality and body weight up to 400 mg Al/kg bw/day	Muller et al., 1990

*with maternal toxicity

- In these feeding studies, aluminium content of basal diet was not determined.

これまでの研究:児の神経行動学的影響

Swiss Websterマウスに乳酸アルミニウムを混餌投与したカリフォルニア大学のグループの論文

投与期間	最小毒性量と主な毒性	文献
妊娠0日−生後21日	400 ppm* 神経行動発生の遅延(生後8−18日)**	Golub et al., 1987
妊娠0日−離乳	500 ug Al/g diet (100 mg Al/kg/day) 足幅、温度感受性、握力 への影響(生後21−39日)	Donald et al. 1989
妊娠中・授乳中	1000 ug Al/g diet (およそ250 mg Al/kg/day) 温度感受性、握力への影響 (生後21)**	Golub et al. 1992b
妊娠開始から離乳または成熟まで	500 ug Al/g diet (50 mg Al/kg/day) 握力への影響 (生後150−170)	Golub et al., 1995
出生前から一生涯	1000 ug Al/g diet (およそ100 mg Al/kg/day) 生後18と24ヶ月の神経行動検査で一貫性のある結果は得られていない	Gloub et al., 2000
妊娠0日 − 生後35日	500 ug Al/g diet (50 mg Al/kg/day) 3か月齢の学習障害、5か月齢の自発運動障害**	Golub & Germann, 2001

NOAEL = 10 mg Al/kg/day

*1日当たりのアルミニウム摂取量のデータなし
**体重低下用量

- 児の身体発達、性成熟に関する情報はこれらの研究結果から得られない。

Previous study: Developmental Neurobehavioral Effects

A group of researchers from the University of California have provided many results in this field. In these studies, Swiss Webster mice were given a diet containing aluminium lactate.

Exposure period	LOAEL & Major toxic effects	Reference
GD0-LD21	400 ppm* Delay in neurobehavioral development (PND8-18)**	Golub et al., 1987
GD0 through weaning	500 ug Al/g diet (100 mg Al/kg/day) Foot splay distance, temperature sensitivity and grip strengths (PND21-39)	Donald et al. 1989
Conception throughout gestation and/or lactation	1000 ug Al/g diet (about 250 mg Al/kg/day) Grasp strength and temperature sensitivity (PND 21)**	Golub et al. 1992b
Conception to weaning or adulthood	500 ug Al/g diet (50 mg Al/kg/day) Grip strength (PND 150-170)	Golub et al., 1995
Conception through lifespan	No consistent differences in neurobehavioural tests at age of 18 and 24 months of age at 1000 ug Al/g diet (about 100 mg Al/kg/day)	Gloub et al., 2000
GD0 - PND35	500 ug Al/g diet (50 mg Al/kg/day) Impaired learning at 3 months of age and motor performance at 5 months of age**	Golub & Germann, 2001

NOAEL = 10 mg Al/kg/day

*no data on daily aluminium intake, **with decreased body weight

- In contrast, insufficient information is available regarding the effects of continuous aluminium exposure on the physical and sexual development of offspring.

アルミニウムの生殖発生毒性に関する最近の報告

被験物質：塩化アルミニウム

動物	投与	最少毒性量と主な毒性	文献
ラット（雄）	飲水、120日間	64 mg/kg bw/day ↓血中テストステロン・卵胞刺激ホルモン・精巣アンドロゲンレセプターmRNA/タンパク発現	Sun et al., 2011,
ラット（雌）	飲水、120日間	64 mg/kg bw/day ↓血中エストラジオール・プロゲストゲン・卵胞刺激ホルモン・黄体形成ホルモン	Wang et al. 2012
ラット（雄）	経口、30-60日間	34 mg/kg bw/day ↓血清テストステロン、↑精巣マロンジアルデヒド, 精子パラメーターの変化、精細管・精巣上体・前立腺の病理組織学的変化	Moselhy et al., 2012
マウス	飲水、妊娠0日-授乳15日	300 mg Al/kg bw/day ↓児生後の体重増加, ↓前脳ドーパミン・セロトニン 発毛・開眼の遅れ、感覚・運動・反射・自発運動・学習能力・認知行動の変化	Abu-Taweel et al. 2012

- これらの研究では、飼料中のアルミニウム含量は測定されていない。

Recent reports on the reproductive/developmental toxicity of aluminium

All of the following studies used aluminium chloride as a test substance.

Animals	Exposure	LOAEL & Major toxic effects	Reference
Rats (male)	120 days, via drinking water	64 mg/kg bw/day serum testosterone↓, serum follicle-stimulating hormone↓, testicular mRNA/protein expressions of androgen receptor↓	Sun et al., 2011,
Rats (female)	120 days, via drinking water	64 mg/kg bw/day blood levels of estradiol↓, progestogen↓, follicle-stimulating hormone↓ and luteinizing hormone↓	Wang et al. 2012
Rats (male)	30-60 days, oral	34 mg/kg bw/day serum testosterone↓, testicular malondialdehyde↑, deteriorated semen picture, histopathological changes of seminiferous tubules, epididymis and prostate gland	Moselhy et al., 2012
Mice	GD0-LD15, via drinking water	300 mg Al/kg bw/day postnatal body weight gain↓, delays in eye opening and hair appearance, and deficits in sensory motor reflexes (PND1-21), locomotor activity (PND22), learning capability (PND25) and cognitive behavior (PND 30-36), forebrain dopamine and serotonin levels ↓(PND7-36)	Abu-Taweel et al. 2012

- In these studies, aluminium content of basal diet was not determined.

アルミニウム塩のラット二世代生殖毒性試験

アルミニウムの評価には発生毒性及び多世代試験が必要（JECFA第67回会議、2006年6月）。

データの不足を補うために

アルミニウムの生殖発生への影響を網羅的に調べるために

OECD TG416及び我が国のガイドライン「食品添加物の指定及び使用基準改正に関する指針」に従って、GLP下で二世代生殖毒性試験を実施した。

Two-Generation Reproductive Toxicity Study of Aluminium Salts in Rats

The JECFA clearly stated the need for further data on the developmental and multigenerational toxicity of aluminium (67th meeting in June 2006).

In order to fill data gap,

Two-generation reproduction toxicity study was performed in accordance with OECD TG 416, and Japanese guidelines for the designation of food additives and for revision of standards for the use of food additives.

All procedures involving the use and care of animals were performed in accordance with the principles for G L P.

2世代生殖毒性試験の位置付け

化学物質の健康影響

生殖発生毒性試験としての位置付け

高次試験 5	4次
神経発生毒性試験 4	3次
生殖発生毒性試験 2 神経毒性試験 3	2次
スクリーニング毒性試験（化審法） 簡易生殖発生毒性試験/ 反復投与毒性・生殖発生毒性併合試験 1	1次

OECDテストガイドライン

1：28日反復投与毒性試験（TG407）＋遺伝毒性試験(TG471, 472, 473)
　簡易生殖発生毒性試験（TG421）＋反復投与毒性・生殖発生毒性併合試験(TG422)

2：出生前発生毒性試験（TG414）＋2世代生殖毒性試験（TG416）

3：げっ歯類の神経毒性試験（TG424）

4：神経発生毒性試験（TG426）

5：より高次の生殖発生毒性試験/発生神経毒性試験

Two-generation reproductive toxicity study

Health effects of chemicals

Reproductive/ developmental toxicity testing

SPECIFIC STUDY 5	Tier 4
Developmental neurotoxicity study 4	Tier 3
Reproductive/developmental toxicity study 2 Neurotoxicity study 3	Tier 2
SCREENING TOXICITY STUDY Reproduction/developmental toxicity screening test Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test 1	Tier 1

OECD Guidelines for the Testing of Chemicals

1：Repeated dose 28-day oral toxicity study in rodents（TG407）＋ Genotoxicity studies (TG471, 472, 473)
　Reproduction/developmental toxicity screening test（TG421）
　＋Combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (TG422)

2：Prenatal development toxicity study（TG414）＋Two-generation reproduction toxicity study（TG416）

3：Neurotoxicity study in rodents（TG424）

4：Developmental neurotoxicity study（TG426）

5：More specific reproductive/developmental toxicity study or developmental neurotoxicity study

試験物質

硫酸アルミニウム（AS）

$Al_2(SO_4)_3$

CAS No. 10043-01-3

- 水溶性（37.5 g/100 mL at 20° C）
- 用途　浄水剤（凝集剤）、サイジング剤、消火器用剤など

環境及び飲料水を介した暴露が懸念される。

硫酸アルミニウムアンモニウム（無水AAS）

$AlNH_4(SO_4)_2$

CAS No.: 7784-25-0（無水物）, 7784-26-1（12水和物）

- 水溶性（14.8 g/100 mL at 20 °C, 12水和物）
- 用途: 食品添加物（ベーカリー製品, 卵製品、ハーブ、香辛料、大豆製品、菓子、加工魚及び野菜製品 、糖果等に、固定剤、膨張剤もしくは安定剤等として）、写真の定着剤、皮革なめし剤など
- AASは、食品添加物に関するCODEX一般規格のTable 1にリストされており、日本では指定添加物に分類されている。

食物からの暴露が懸念される。

TEST SUBSTANCES

Aluminium sulfate (AS)

$Al_2(SO_4)_3$

CAS No. 10043-01-3

- Water soluble salt of aluminium (37.5 g/100 mL at 20°C)
- Application: flocculant for water purification, paper sizing agent, fire extinguisher materials, etc.

The use of AS could lead to aluminium exposure to aluminium via drinking water or via the environment in the general population.

$AlNH_4(SO_4)_2$

Aluminium ammonium sulfate (AAS, anhydrous)

CAS No.: 7784-25-0 (anhydrous), 7784-26-1 (dodecahydrate)

- Water soluble salt of aluminium (14.8 g/100 mL at 20 °C, dodecahydrate)
- Application: food additive (firming agent, raising agent or stabilizer in bakery products, egg products, herbs and spices, soya-bean products, snacks, processed fish, processed vegetables and candied fruit), fixing agent in photography, leather tanning agent, etc.
- AAS is listed in table 1 of the CODEX general standard for food additives, and classified as a designated food additive in Japan.

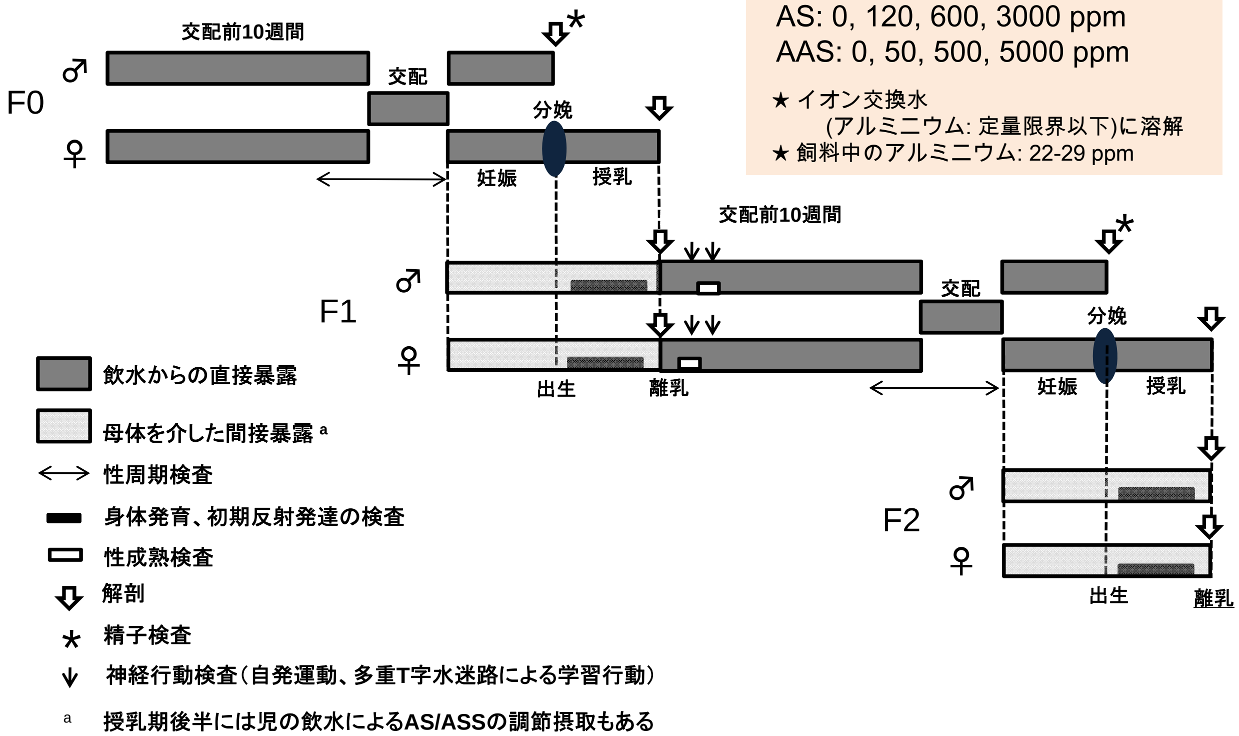
The use of AAS would lead to dietary exposure of the general population to aluminium.

実験計画

Crl:CD(SD)ラット(各群雌雄24匹)に硫酸アルミニウム(AS)または硫酸アルミニウムアンモニウム(AAS)を2世代にわたって飲水投与した。

飲料水中の濃度
AS: 0, 120, 600, 3000 ppm
AAS: 0, 50, 500, 5000 ppm

★ イオン交換水
(アルミニウム: 定量限界以下)に溶解
★ 飼料中のアルミニウム: 22-29 ppm

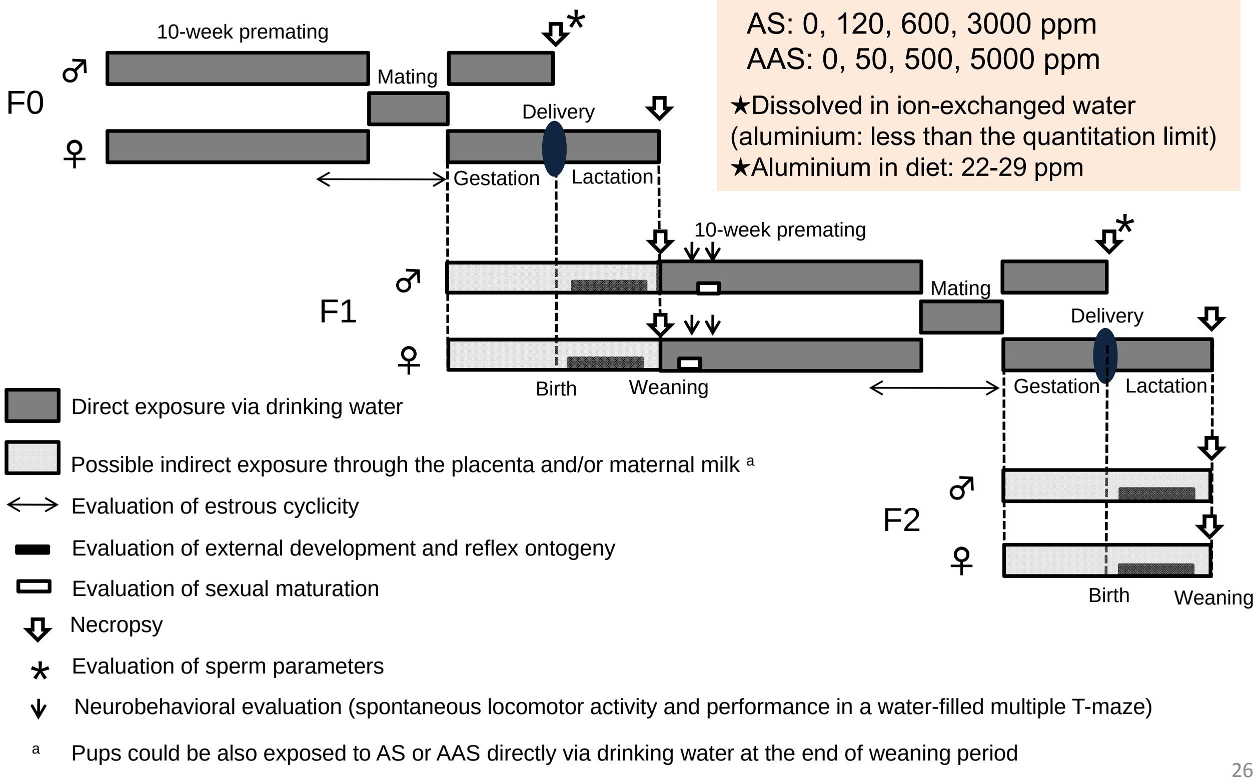


Experimental Design

Crl:CD(SD) rats (24/sex/dose) were given AS or AAS in drinking water throughout two generations.

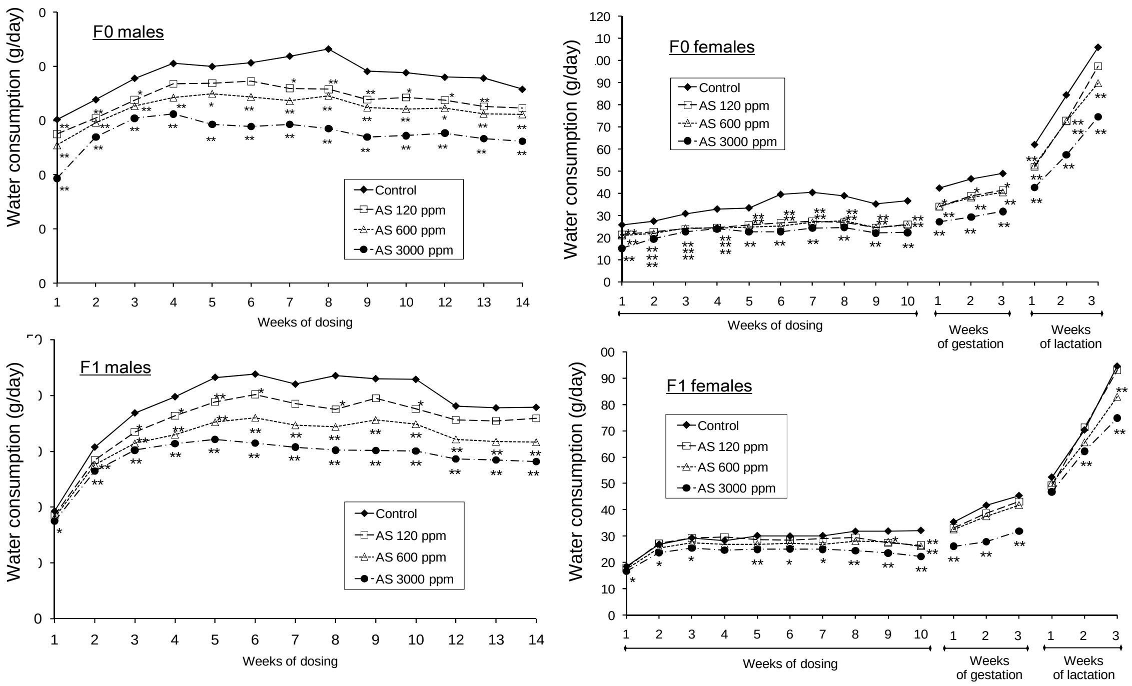
Concentrations in drinking water
AS: 0, 120, 600, 3000 ppm
AAS: 0, 50, 500, 5000 ppm

★Dissolved in ion-exchanged water
(aluminium: less than the quantitation limit)
★Aluminium in diet: 22-29 ppm



硫酸アルミニウム (AS) の試験結果（親動物の飲水量）

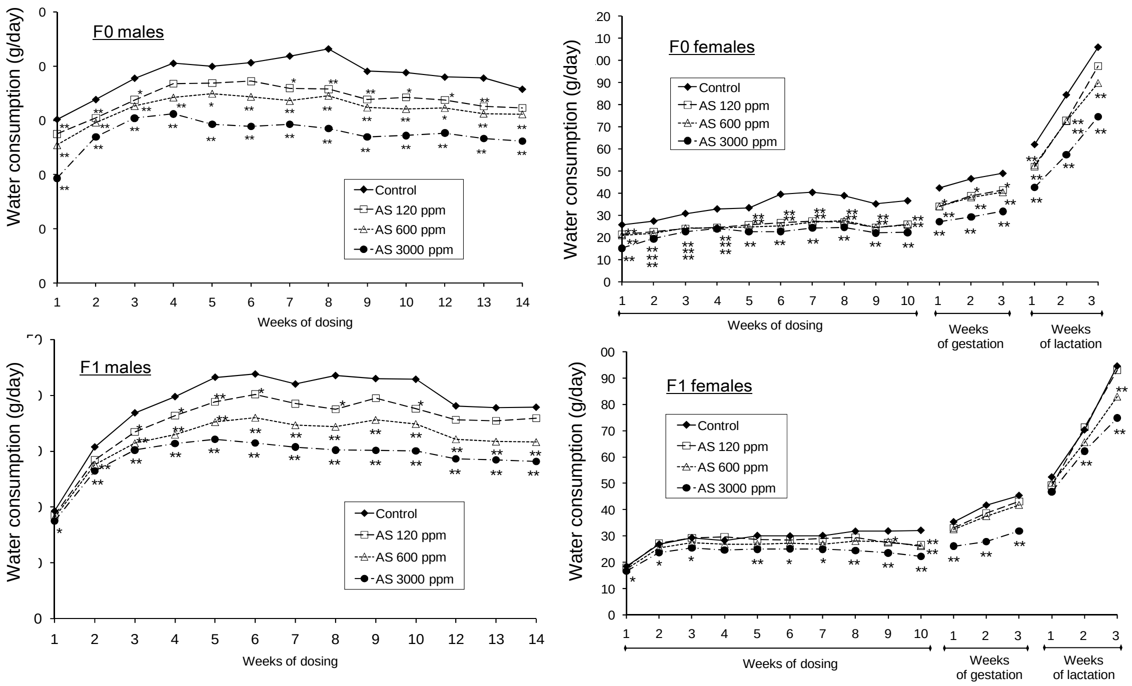
Water consumption



Results for Aluminium Sulfate (AS)

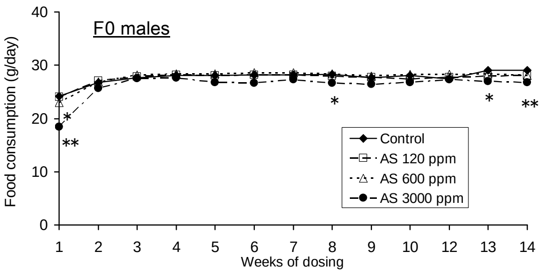
PARENTAL EFFECTS

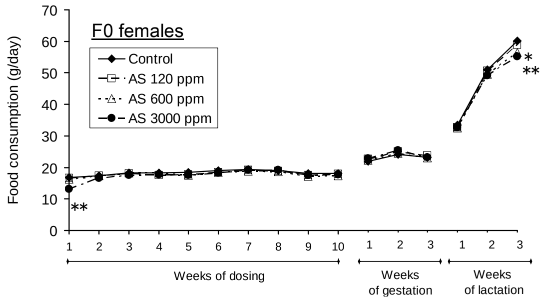
Water consumption

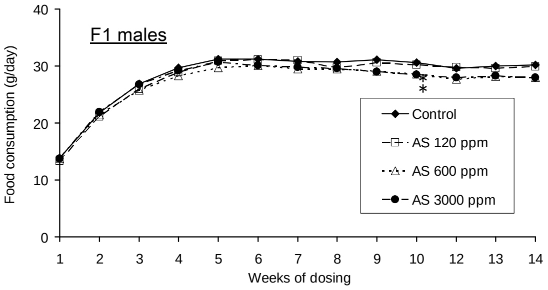


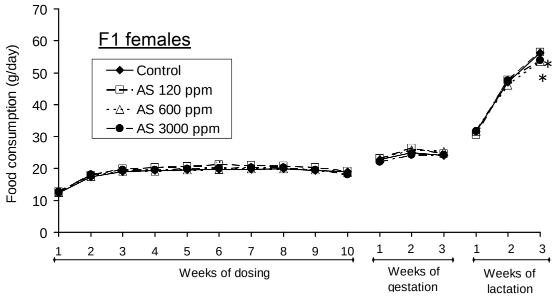
硫酸アルミニウム (AS) の試験結果（親動物の摂餌量）

Food consumption





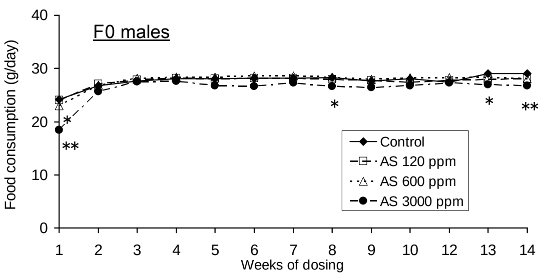


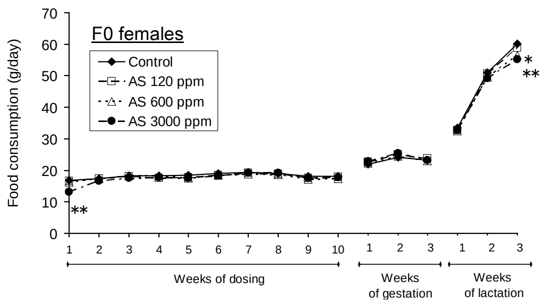


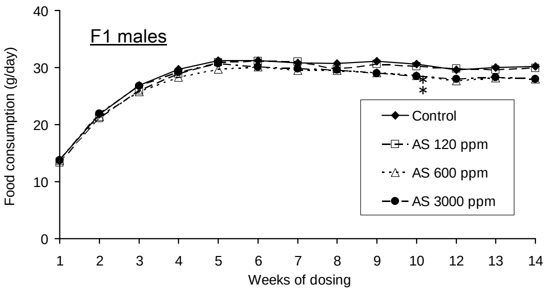
Results for Aluminium Sulfate (AS)

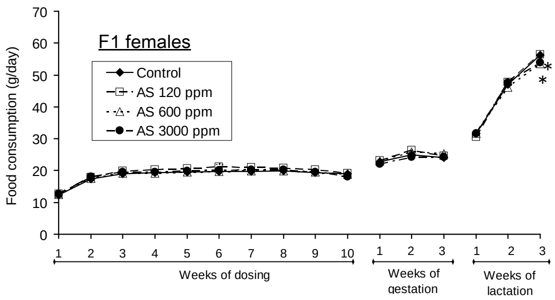
PARENTAL EFFECTS

Food consumption



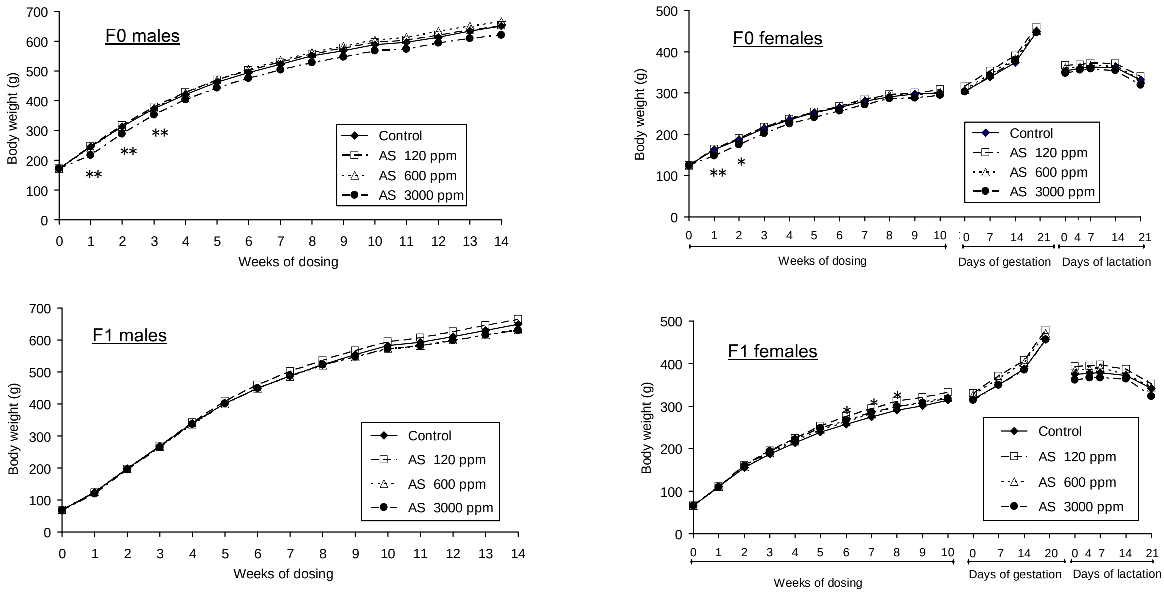






硫酸アルミニウム (AS) の試験結果（親動物の体重）

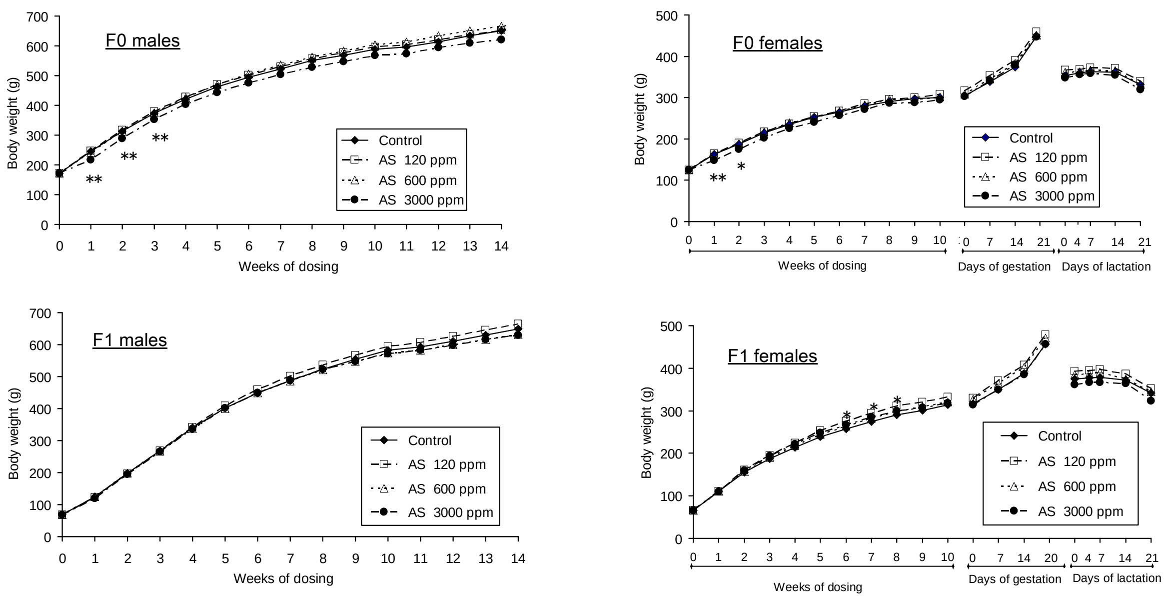
Body weight



Results for Aluminium Sulfate (AS)

PARENTAL EFFECTS

Body weight



F0及び F1動物の１日当たりの平均アルミニウム摂取量

	飲水中AS (ppm)	F0世代 AS摂取量 (mg/kg bw/day)	F0世代 Al 摂取量[a] (mg Al/kg bw/day)	F1世代 AS摂取量 (mg/kg bw/day)	F1世代 Al 摂取量[a] (mg Al/kg bw/day)
雄					
全試験期間	0	0	1.62	0	1.93
	120	8.65	2.96	10.7	3.55
	600	41.0	8.06	50.2	9.78
	3000	188	31.2	232	38.5
雌					
交配前期間	0	0	2.05	0	2.26
	120	12.2	3.92	14.2	4.50
	600	60.4	11.5	69.7	13.2
	3000	282	46.5	316	52.1
妊娠中	0	0	1.63	0	1.64
	120	11.4	3.42	11.0	3.44
	600	57.5	10.7	54.2	10.2
	3000	227	37.5	217	35.9
授乳中	0	0	3.73	0	3.37
	120	24.9	7.51	22.9	6.86
	600	123	22.9	109	20.4
	3000	515	84.8	530	87.0

a 飼料及び飲水中のアルミニウムを加えた、総摂取量
(basal diet containing 25-29 ppm aluminium) combined.

Mean Daily Intake of AS and Aluminium by F0 and F1 Males and Females throughout Exposure

	AS in drinking water (ppm)	F0 generation AS intake (mg/kg bw/day)	F0 generation Al intake[a] (mg Al/kg bw/day)	F1 generation AS intake (mg/kg bw/day)	F1 generation Al intake[a] (mg Al/kg bw/day)
Males					
Whole period	0	0	1.62	0	1.93
	120	8.65	2.96	10.7	3.55
	600	41.0	8.06	50.2	9.78
	3000	188	31.2	232	38.5
Females					
Premating	0	0	2.05	0	2.26
	120	12.2	3.92	14.2	4.50
	600	60.4	11.5	69.7	13.2
	3000	282	46.5	316	52.1
Gestation	0	0	1.63	0	1.64
	120	11.4	3.42	11.0	3.44
	600	57.5	10.7	54.2	10.2
	3000	227	37.5	217	35.9
Lactation	0	0	3.73	0	3.37
	120	24.9	7.51	22.9	6.86
	600	123	22.9	109	20.4
	3000	515	84.8	530	87.0

a Total ingested dose of aluminium from drinking water and food
(basal diet containing 25-29 ppm aluminium) combined.

硫酸アルミニウム（AS）の実験結果（生殖発生指標）

交尾・受胎・出産率、同居から妊娠までの日数、妊娠期間、着床・分娩児数、形態異常児頻度、性周期、精子検査結果、雌雄の親動物の生殖器官の病理組織学的検査結果に投与による有害影響は認められなかった。

生殖指標

AS (ppm)		0 (control)	120	600	3000
F0 generation					
No. of rats (male/female)		24/24	24/24	24/24	24/24
Copulation index (%) [a]	Males	91.7	91.7	100	91.7
	Females	95.8	100	100	100
Precoital interval (days) [b]		3.2 ±1.1	3.2 ±1.8	2.9 ±1.3	2.8 ±1.6
Fertility index (%) [c]	Males	95.5	90.9	100	95.5
	Females	95.7	91.7	100	95.8
Gestation index (%) [d]		100	95.5	95.7	95.7
Gestation length (days) [b]		22.4 ±0.5	22.5 ±0.6	22.1 ±0.4	22.3 ±0.5
Delivery index (%) [b,e]		94.3 ±5.6	88.6 ±21	90.7 ±20.8	92.0 ±20.5
F1 generation					
No. of rats (male/female)		24/24	23/24	24/24	24/24
Copulation index (%) [a]	Males	95.8	91.3	95.8	87.5
	Females	100	95.8	100	95.8
Precoital interval (days) [b]		3.3 ±3.2	3.0 ±2	2.7 ±1.5	2.3 ±1.1
Fertility index (%) [c]	Males	91.3	81	91.3	95.2
	Females	91.7	82.6	91.7	91.3
Gestation index (%) [d]		100	94.7	100	100
Gestation length (days) [b]		22.4 ±0.5	22.3 ±0.5	22.2 ±0.4	22.2 ±0.4
Delivery index (%) [b,e]		94.0 ±9.9	87.5 ±22.6	91.4 ±10.7	94.6 ±6.8

a Copulation index (%) = (no. of animals with successful copulation/no. of animals paired
b Values are given as the mean ± S.D.
c Fertility index (%) = (no. of animals that impregnated a female or were pregnant/no. of animals with successful copulation) × 100.
d Gestation index (%) = (no. of females that delivered live pups/no. of pregnant females)
e Delivery index (%) = (no. of pups delivered/no. of implantations) × 100.

発生指標

AS (ppm)	0 (control)	120	600	3000
F1 offspring				
No. of litters	22	21	22	22
No. of pups delivered [a]	13.9 ±1.7	12.4 ±4.7	13.1 ±4.1	13.1 ±3.4
Sex ratio of pups [b]	0.503	0.462	0.513	0.536
Viability index of pups (%) [a]				
on PND 0 [c]	100.0 ±0.0	99.3 ±2.3	99.7 ±1.6	99.5 ±2.4
on PND 4 [d]	98.7 ±2.9	95.2 ±21.8	98.8 ±2.6	98.0 ±5.4
on PND 21 [e]	99.4 ±2.7	100.0 ±0.0	100.0 ±0.0	99.4 ±2.7
F2 offspring				
No. of litters	22	18	22	21
No. of pups delivered [a]	13.1 ±3.6	13.2 ±3.8	12.6 ±3.9	14.0 ±1.9
Sex ratio of pups [b]	0.528	0.502	0.536	0.457
Viability index of pups (%) [a]				
on PND 0 [c]	99.68 ±1.51	99.49 ±2.14	98.42 ±3.57	98.69 ±3.6
on PND 4 [d]	94.72 ±14.54	98.07 ±5.45	99.07 ±3.15	99.01 ±2.49
on PND 21 [e]	100.00 ±0.00	98.61 ±4.04	100.00 ±0.00	100.00 ±0.00

a Values are given as the mean ± S.D.
b Sex ratio = total no. of male pups/total no. of pups.
c Viability index on PND 0 (%) = (no. of live pups on PND 0/no. of pups delivered) × 100.
d Viability index on PND 4 (%) = (no. of live pups on PND 4/no. of live pups on PND 0) × 100.
e Viability index on PND 21 (%) = (no. of live pups on PND 21/no. of live pups on PND 4 after cull) × 100.
* Significantly different from the control, $P < 0.05$, **: Significantly different from the control, $P < 0.01$

Results for Aluminium Sulfate (AS)

Reproductive and Developmental Toxicity

Continuous drinking of AS-contained water for two generations did not result in changes in copulation, fertility or gestation indices, pre-coital or gestation length, the number of implantations or pups delivered, or the incidence of pups with malformations or variations. In addition, adverse effects were not found in estrous cyclicity or sperm parameters, and the histopathology of reproductive tissues in male and female parental animals.

Reproductive performance

AS (ppm)		0 (control)	120	600	3000
F0 generation					
No. of rats (male/female)		24/24	24/24	24/24	24/24
Copulation index (%) [a]	Males	91.7	91.7	100	91.7
	Females	95.8	100	100	100
Precoital interval (days) [b]		3.2 ±1.1	3.2 ±1.8	2.9 ±1.3	2.8 ±1.6
Fertility index (%) [c]	Males	95.5	90.9	100	95.5
	Females	95.7	91.7	100	95.8
Gestation index (%) [d]		100	95.5	95.7	95.7
Gestation length (days) [b]		22.4 ±0.5	22.5 ±0.6	22.1 ±0.4	22.3 ±0.5
Delivery index (%) [b,e]		94.3 ±5.6	88.6 ±21	90.7 ±20.8	92.0 ±20.5
F1 generation					
No. of rats (male/female)		24/24	23/24	24/24	24/24
Copulation index (%) [a]	Males	95.8	91.3	95.8	87.5
	Females	100	95.8	100	95.8
Precoital interval (days) [b]		3.3 ±3.2	3.0 ±2	2.7 ±1.5	2.3 ±1.1
Fertility index (%) [c]	Males	91.3	81	91.3	95.2
	Females	91.7	82.6	91.7	91.3
Gestation index (%) [d]		100	94.7	100	100
Gestation length (days) [b]		22.4 ±0.5	22.3 ±0.5	22.2 ±0.4	22.2 ±0.4
Delivery index (%) [b,e]		94.0 ±9.9	87.5 ±22.6	91.4 ±10.7	94.6 ±6.8

a Copulation index (%) = (no. of animals with successful copulation/no. of animals paired
b Values are given as the mean ± S.D.
c Fertility index (%) = (no. of animals that impregnated a female or were pregnant/no. of animals with successful copulation) × 100.
d Gestation index (%) = (no. of females that delivered live pups/no. of pregnant females)
e Delivery index (%) = (no. of pups delivered/no. of implantations) × 100.

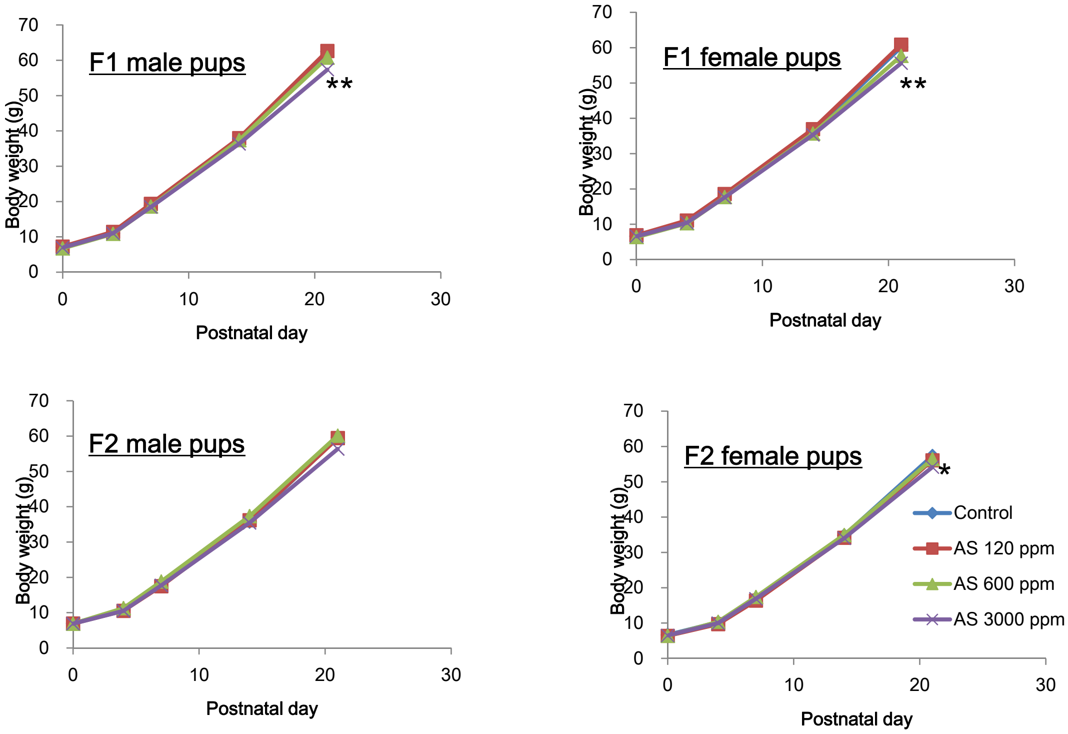
Number of pups delivered, sex ratio and viability

AS (ppm)	0 (control)	120	600	3000
F1 offspring				
No. of litters	22	21	22	22
No. of pups delivered [a]	13.9 ±1.7	12.4 ±4.7	13.1 ±4.1	13.1 ±3.4
Sex ratio of pups [b]	0.503	0.462	0.513	0.536
Viability index of pups (%) [a]				
on PND 0 [c]	100.0 ±0.0	99.3 ±2.3	99.7 ±1.6	99.5 ±2.4
on PND 4 [d]	98.7 ±2.9	95.2 ±21.8	98.8 ±2.6	98.0 ±5.4
on PND 21 [e]	99.4 ±2.7	100.0 ±0.0	100.0 ±0.0	99.4 ±2.7
F2 offspring				
No. of litters	22	18	22	21
No. of pups delivered [a]	13.1 ±3.6	13.2 ±3.8	12.6 ±3.9	14.0 ±1.9
Sex ratio of pups [b]	0.528	0.502	0.536	0.457
Viability index of pups (%) [a]				
on PND 0 [c]	99.68 ±1.51	99.49 ±2.14	98.42 ±3.57	98.69 ±3.6
on PND 4 [d]	94.72 ±14.54	98.07 ±5.45	99.07 ±3.15	99.01 ±2.49
on PND 21 [e]	100.00 ±0.00	98.61 ±4.04	100.00 ±0.00	100.00 ±0.00

a Values are given as the mean ± S.D.
b Sex ratio = total no. of male pups/total no. of pups.
c Viability index on PND 0 (%) = (no. of live pups on PND 0/no. of pups delivered) × 100.
d Viability index on PND 4 (%) = (no. of live pups on PND 4/no. of live pups on PND 0) × 100.
e Viability index on PND 21 (%) = (no. of live pups on PND 21/no. of live pups on PND 4 after cull) × 100.
* Significantly different from the control, $P < 0.05$, **: Significantly different from the control, $P < 0.01$

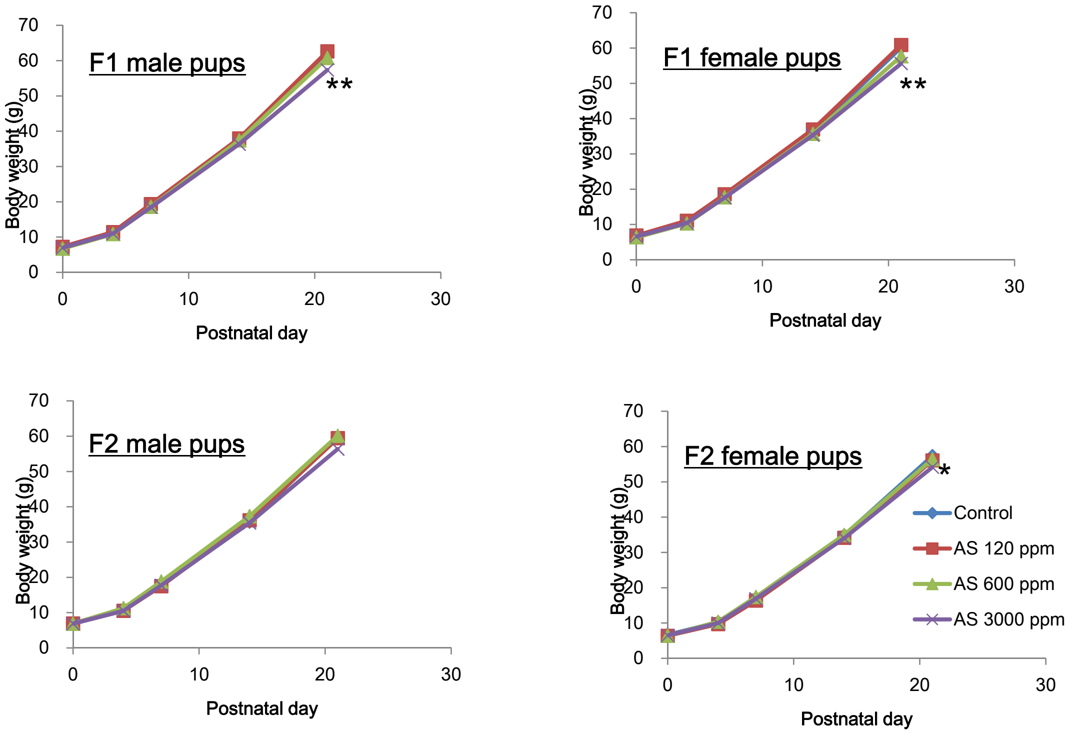
硫酸アルミニウム（AS）の実験結果（児動物の体重）

Body weights of F1 and F2 pups



Results for Aluminium Sulfate (AS)

Body weights of F1 and F2 pups



硫酸アルミニウム（AS）の実験結果（離乳児動物の器官重量 ）

3000ppmにおいて、様々の器官重量の変化が観察された。そのうち、脳比体重重量の増加は、絶対重量に変化がなかったことから体重低下に起因すると考えられた。腎臓、精巣、精巣上体、子宮等の比体重重量の変化を伴わない絶対重量の低下も、体重低下に起因するものと考えられた。一方で、胸腺、肝臓、脾臓では、絶対及び比重量が共に低下した。

Sex		Males				Females			
AS (ppm)		0 (Control)	120	600	3000	0 (Control)	120	600	3000
F1									
Thymus	(mg)	375 ±55	384 ±86	357 ±58	305 ±51**	383 ±66	373 ±74	345 ±46	313 ±33**
	(mg/100 g b.w.)	414 ±56	409 ±64	398 ±59	383 ±36	453 ±63	433 ±64	429 ±57	415 ±41
Liver	(g)	4.33 ±0.43	4.40 ±0.6	4.22 ±0.45	3.49 ±0.53**	3.83 ±0.47	3.92 ±0.48	3.61 ±0.35	3.24 ±0.34**
	(g/100 g b.w.)	4.77 ±0.3	4.71 ±0.33	4.70 ±0.27	4.37 ±0.30**	4.53 ±0.3	4.57 ±0.31	4.48 ±0.3	4.27 ±0.25*
Spleen	(mg)	394 ±49	410 ±68	388 ±74	301 ±43**	337 ±62	356 ±55	341 ±64	292 ±43*
	(mg/100 g b.w.)	436 ±63	437 ±40	432 ±73	379 ±37**	400 ±67	415 ±44	422 ±53	386 ±47
F2									
Thymus	(mg)	382 ±50	348±49	357 ±66	305 ±56**	337 ±45	364 ±36	347 ±49	312 ±37
	(mg/100 g b.w.)	439 ±70	392 ±52*	411 ±57	386 ±40**	419 ±61	457 ±50	431 ±47	424 ±54
Liver	(g)	3.93 ±0.37	4.04 ±0.64	3.91 ±0.39	3.45 ±0.41**	3.56 ±0.35	3.61 ±0.39	3.61 ±0.48	3.07 ±0.26**
	(g/100 g b.w.)	4.49 ±0.34	4.52 ±0.44	4.50 ±0.24	4.36 ±0.23	4.41 ±0.21	4.51 ±0.26	4.47 ±0.26	4.17 ±0.29**
Spleen	(mg)	368 ±54	381 ±62	361 ±49	296 ±48**	321 ±47	332 ±59	331 ±57	270 ±55**
	(mg/100 g b.w.)	421 ±64	427 ±50	416 ±48	372 ±42**	398 ±59	415 ±64	409 ±42	365 ±67

*: Significantly different from the control, *P* <0.05; **: Significantly different from the control, P

◎　肝臓及び脾臓の病理組織に変化は見られなかった.

Results for Aluminium Sulfate (AS)

Organ weights of F1 and F2 weanlings

Various organ weight changes were found in the 3000ppm group. Among them, an increase in the relative brain weight is considered to be a secondary change that occurs with the fall in body weight because the absolute weight did not change. Similarly, decreased absolute weights of the kidneys, testes, epididymides, uterus, etc., without changes in the relative weight, were thought to be associated with decreased body weight. On the other hand, for the thymus, liver and spleen, both absolute and relative weights were decreased as follows.

Sex		Males				Females			
AS (ppm)		0 (Control)	120	600	3000	0 (Control)	120	600	3000
F1									
Thymus	(mg)	375 ±55	384 ±86	357 ±58	305 ±51**	383 ±66	373 ±74	345 ±46	313 ±33**
	(mg/100 g b.w.)	414 ±56	409 ±64	398 ±59	383 ±36	453 ±63	433 ±64	429 ±57	415 ±41
Liver	(g)	4.33 ±0.43	4.40 ±0.6	4.22 ±0.45	3.49 ±0.53**	3.83 ±0.47	3.92 ±0.48	3.61 ±0.35	3.24 ±0.34**
	(g/100 g b.w.)	4.77 ±0.3	4.71 ±0.33	4.70 ±0.27	4.37 ±0.30**	4.53 ±0.3	4.57 ±0.31	4.48 ±0.3	4.27 ±0.25*
Spleen	(mg)	394 ±49	410 ±68	388 ±74	301 ±43**	337 ±62	356 ±55	341 ±64	292 ±43*
	(mg/100 g b.w.)	436 ±63	437 ±40	432 ±73	379 ±37**	400 ±67	415 ±44	422 ±53	386 ±47
F2									
Thymus	(mg)	382 ±50	348±49	357 ±66	305 ±56**	337 ±45	364 ±36	347 ±49	312 ±37
	(mg/100 g b.w.)	439 ±70	392 ±52*	411 ±57	386 ±40**	419 ±61	457 ±50	431 ±47	424 ±54
Liver	(g)	3.93 ±0.37	4.04 ±0.64	3.91 ±0.39	3.45 ±0.41**	3.56 ±0.35	3.61 ±0.39	3.61 ±0.48	3.07 ±0.26**
	(g/100 g b.w.)	4.49 ±0.34	4.52 ±0.44	4.50 ±0.24	4.36 ±0.23	4.41 ±0.21	4.51 ±0.26	4.47 ±0.26	4.17 ±0.29**
Spleen	(mg)	368 ±54	381 ±62	361 ±49	296 ±48**	321 ±47	332 ±59	331 ±57	270 ±55**
	(mg/100 g b.w.)	421 ±64	427 ±50	416 ±48	372 ±42**	398 ±59	415 ±64	409 ±42	365 ±67

*: Significantly different from the control, *P* <0.05; **: Significantly different from the control, P

◎　No histopathological changes were detected in the liver and spleen.

硫酸アルミニウム（AS）の実験結果（児動物の発達指標 ）

3000 ppm投与群においてF1動物の膣開口のわずかな遅延が認められたが、包皮分離を含め他の発達指標には投与の影響は認められなかった。

Sexual development of F1 males and females

AS (ppm)	0 (control)	120	600	3000
Male preputial separation				
No. of males examined	24	24	24	24
Age (days)	40.7 ± 1.6	40.8 ± 1.0	40.3 ± 1.3	40.5 ± 1.9
Body weight (g)	243.5 ± 23.8	239.9 ± 24.8	232.9 ± 20.4	229.1 ± 19.2
Female vaginal opening				
No. of females examined	24	24	24	24
Age (days)	29.5 ± 2.1	30.0 ± 2.3	30.5 ± 1.8	31.4 ± 1.7**
Body weight (g)	109.6 ± 11.6	113.6 ± 15.4	114.6 ± 15.1	119.0 ± 13.3

Values are given as the mean ± SD.
** Significantly different from the control, $P < 0.01$.

膣開口遅延がみられた雌ラットは正常な生殖能力を示し、肛門生殖突起間距離（AGD）、性周期、生殖器官の重量・病理組織学的所見にも投与の影響は認められなかったことから、アルミニウムはホルモンに関連する指標に明らかな影響を及ぼさないと考えられた。

Results for Aluminium Sulfate (AS)

Effects on the developmental landmarks

Vaginal opening was slightly delayed in F1 females in the 3000ppm group while no compound-related changes were found in the other developmental landmarks, including male preputial separation.

Sexual development of F1 males and females

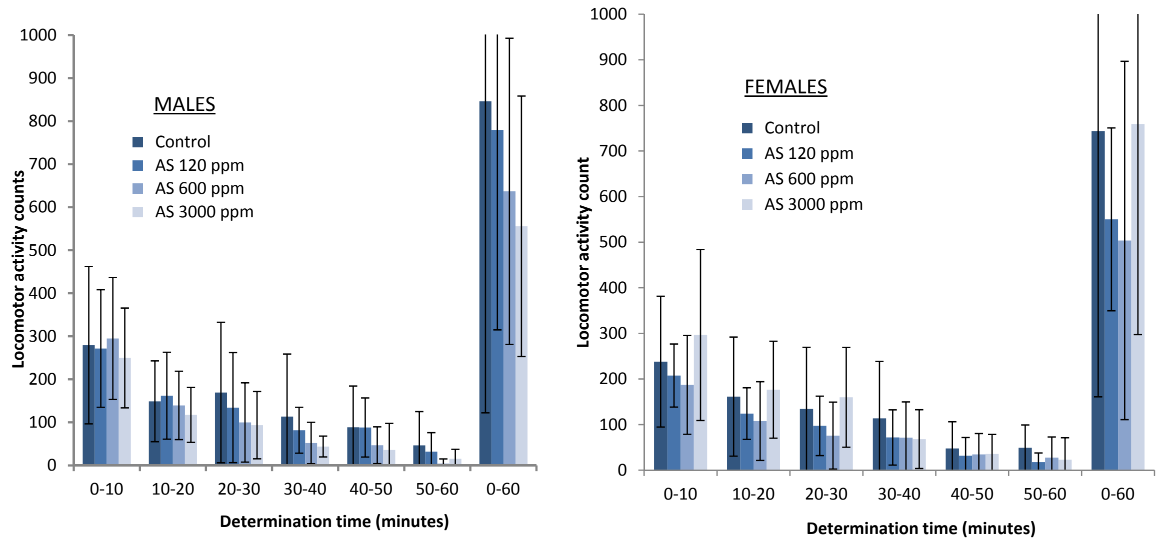
AS (ppm)	0 (control)	120	600	3000
Male preputial separation				
No. of males examined	24	24	24	24
Age (days)	40.7 ± 1.6	40.8 ± 1.0	40.3 ± 1.3	40.5 ± 1.9
Body weight (g)	243.5 ± 23.8	239.9 ± 24.8	232.9 ± 20.4	229.1 ± 19.2
Female vaginal opening				
No. of females examined	24	24	24	24
Age (days)	29.5 ± 2.1	30.0 ± 2.3	30.5 ± 1.8	31.4 ± 1.7**
Body weight (g)	109.6 ± 11.6	113.6 ± 15.4	114.6 ± 15.1	119.0 ± 13.3

Values are given as the mean ± SD.
** Significantly different from the control, $P < 0.01$.

Rats with delayed vaginal opening progressed to showing normal reproductive capacity and outcome. In addition, no effects were found on AGD, estrous cyclicity or on the weight and histopathology of reproductive organs in weanlings and adults. It seems unlikely that aluminium has a clear impact on hormonal events.

硫酸アルミニウム（AS）の実験結果（自発運動）

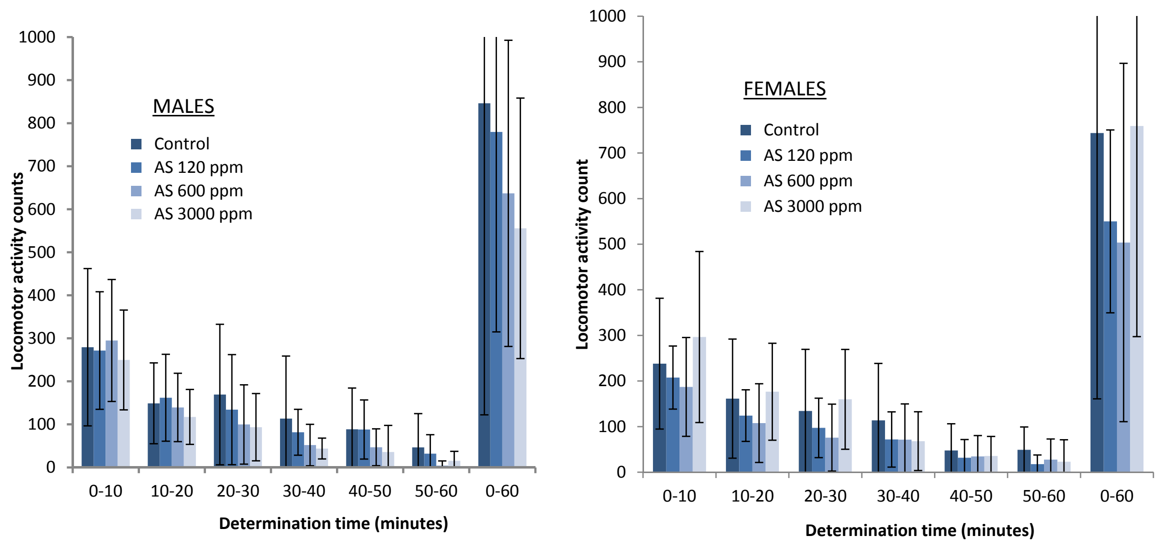
F1親動物の自発運動



F1・F2動物の反射発現、F1動物の自発運動には投与の影響は認められなかった。

Results for Aluminium Sulfate (AS)

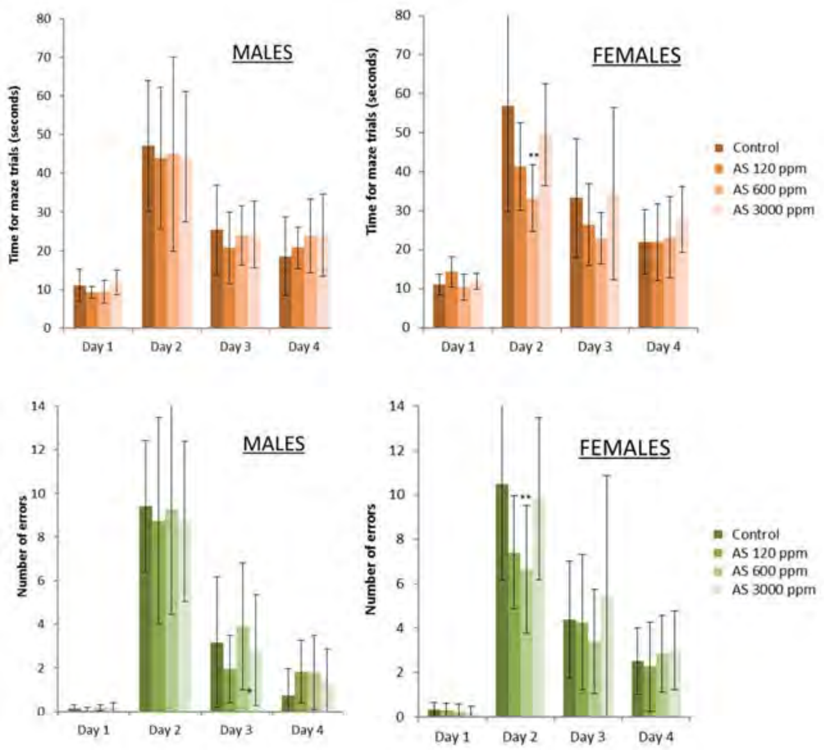
Locomotor activity count in F1 parental rats



No changes were found in the reflex ontogeny of F1 and F2 pups and in spontaneous locomotor activity tested at 4 weeks of age for F1 animals.

硫酸アルミニウム（AS）の実験結果（水迷路試験 ）

F1ラットの水迷路試験結果



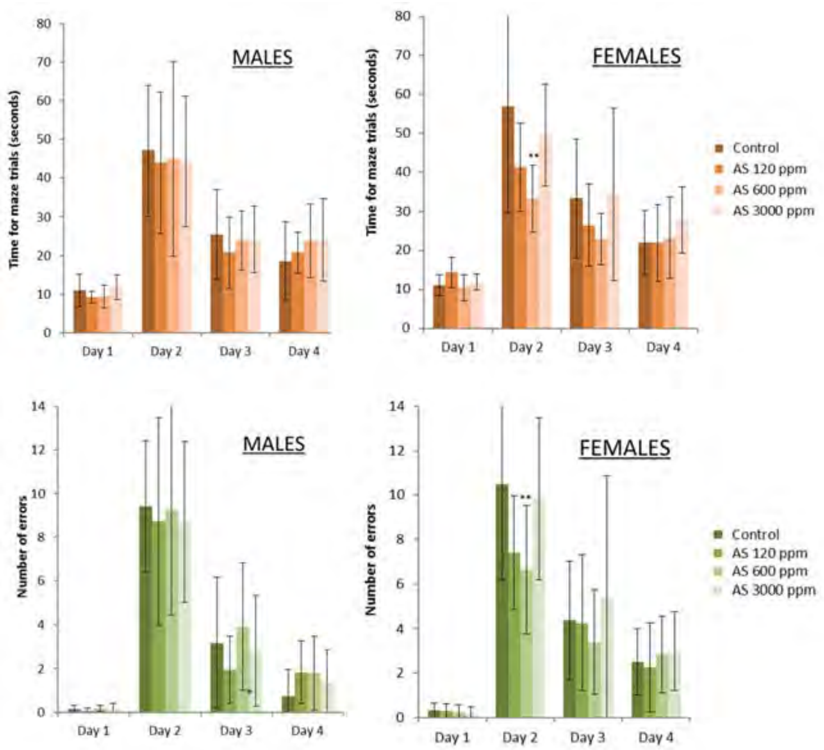
**Significantly different from the control, P<0.01

600 ppmでゴールに達するまでの時間及びエラー数が一過性に短縮/減少したが、用量依存性は認められなかったことから、投与の影響とは考えられなかった。

これまでの報告で認められている神経行動学的変化は、本研究よりも高濃度のアルミニウムを摂取した結果によると考えられる。

Results for Aluminium Sulfate (AS)

Performance in a water-filled multiple T-maze in F1 parental rats



**Significantly different from the control, P<0.01

A transient decrease in the elapsed time and the number of errors in females in the 600ppm group was not considered to be treatment-related because of the lack of dose-dependency.

These findings indicate that previous findings of developmental neurotoxic effects were possibly related to the toxic effects of aluminium given at higher doses than those given in this study.

硫酸アルミニウム（AS）実験結果のまとめ

	F0親/F1 児			F1親/F2児		
AS (ppm)	120	600	3000	120	600	3000
<u>親動物に対する影響</u>						
飲水量	↓	↓	↓	↓	↓	↓
摂餌量	－	↓	↓	－	↓	↓
体重	－	－	↓	－	－	－
<u>児動物に対する影響</u>						
授乳中の体重	－	－	↓	－	－	↓
胸腺重量	－	－	↓	－	－	↓
肝臓重量	－	－	↓	－	－	↓
脾臓重量	－	－	↓	－	－	↓
膣開口	－	－	Delay (1.9 days)	n.d.	n.d.	n.d.

親動物及び生殖発生毒性の無毒性量は600 ppm (41.0 mg/kg bw/day)であり、飲水及び餌由来のアルミニウムを加えた総アルミニウム摂取量は8.06 mg Al/kg bw/dayであった。

Summary of Results for Aluminium Sulfate (AS)

	F0/F1 generation			F1/F2 generation		
AS (ppm)	120	600	3000	120	600	3000
<u>Effects on parental animals</u>						
Water consumption	↓	↓	↓	↓	↓	↓
Food consumption	-	↓	↓	-	↓	↓
Body weight	-	-	↓	-	-	-
<u>Effects on pups</u>						
Pup weight during lactation	-	-	↓	-	-	↓
Thymus weight	-	-	↓	-	-	↓
Liver weight	-	-	↓	-	-	↓
Spleen weight	-	-	↓	-	-	↓
Day of vaginal opening	-	-	Delay (1.9 days)	n.d.	n.d.	n.d.

The no observed adverse effect level was concluded to be 600 ppm (41.0 mg/kg bw/day) for parental systemic toxicity and reproductive/developmental toxicity. The total ingested dose of aluminium from food and drinking water combined in this 600 ppm group was calculated to be **8.06 mg Al/kg bw/day**.

硫酸アルミニウムアンモニウム(AAS)実験結果のまとめ

	F0親/F1児			F1親/F2児		
AAS (ppm)	50	500	5000	50	500	5000
<u>親動物に対する影響</u>						
飲水量	↓	↓	↓	↓	↓	↓
摂餌量	–	↓	↓	–	–	↓
体重	–	–	↓	–	–	↓
<u>児動物に対する影響</u>						
授乳中体重	–	–	↓	–	–	–
胸腺重量	–	–	↓	–	–	↓
肝臓重量	–	–	↓	–	–	↓
脾臓重量	–	–	↓	–	–	↓
膣開口	–	–	Delay (2.1 days)	n.d.	n.d.	n.d.

親動物及び生殖発生毒性の無毒性量は500 ppm (33.5 mg/kg bw/day)であり、飲水及び餌由来のアルミニウムを加えた総アルミニウム摂取量は**5.35 mg Al/kg bw/day**であった。

Summary of Results for Aluminium Ammonium Sulfate (AAS)

	F0/F1 generation			F1/F2 generation		
AAS (ppm)	50	500	5000	50	500	5000
<u>Effects on parental animals</u>						
Water consumption	↓	↓	↓	↓	↓	↓
Food consumption	-	↓	↓	-	-	↓
Body weight	-	-	↓	-	-	↓
<u>Effects on pups</u>						
Pup weight during lactation	-	-	↓	-	-	-
Thymus weight	-	-	↓	-	-	↓
Liver weight	-	-	↓	-	-	↓
Spleen weight	-	-	↓	-	-	↓
Day of vaginal opening	-	-	Delay (2.1 days)	n.d.	n.d.	n.d.

The no observed adverse effect level was concluded to be 500 ppm (33.5 mg/kg bw/day) for parental systemic toxicity and reproductive/developmental toxicity. The total ingested dose of aluminium from food and drinking water combined in this 500 ppm group was calculated to be **5.35 mg Al/kg bw/day**.

結 論

硫酸アルミニウム（AS）または硫酸アルミニウムアンモニウム（AAS）を飲水投与したところ、飲水量の減少が観察され、摂餌量の低下及び体重低下の原因と考えられた。最高投与量では、雌雄の児に低体重がみられ、膣開口の遅れが観察された。しかしながら、生殖、神経行動学的指標には投与の影響は認められなかった。

これらの知見から、生殖発生毒性の無毒性量（NOAEL）は、ASについては600 ppm (41.0 mg/kg bw/day) 、AASについては500 ppm (33.5 mg/kg bw/day)と考えられた。飲水及び餌由来のアルミニウムを加えた総アルミニウム摂取量は、ASについては 8.06 mg Al/kg bw/day、AASについては5.35 mg Al/kg bw/dayであった。

第74回JECFA（2012年6月）においては、二世代生殖毒性試験で観察された離乳前の児体重低下は、飲水量低下に起因した二次的影響と判断し、NOAEL　30 mg/kg bw/dayに 安全係数100を適用して、暫定週間耐容摂取量（PTWI）を2 mg/kgとした。

Conclusions

AS and AAS administered via drinking water resulted in decreased water consumption. This change was associated with decreased food consumption and decreased body weight. In the highest dose group, male and female pups had a lower body weight. At this dose, vaginal opening was slightly delayed. No definitive effects were found in the other reproductive/developmental parameters, including developmental neurobehavioral toxicity.

Based on these considerations, a conservative evaluation of the data led to the conclusion that the no observed adverse effect level of AS and AAS for reproductive and developmental toxicity is 600 ppm (41.0 mg/kg bw/day) and 500 ppm (33.5 mg/kg bw/day), respectively. The total ingested dose of aluminium from food and drinking water combined in the 600 ppm group (AS) and 500 ppm group (AAS) was calculated to be 8.06 mg Al/kg bw/day and 5.35 mg Al/kg bw/day.

In the 74th meeting of JECFA held in June 2011, the Committee concluded that the effects on preweaning body weight observed in the two-generation studies were secondary effects due to decreased water consumption, and established a provisional tolerable weekly intake (PTWI) of 2 mg/kg body weight based on a no-observed-adverse-effect level (NOAEL) of 30 mg/kg body weight per day and application of a safety factor of 100.

ご清聴ありがとうございました。

Thank you very much for your kind attention.