試験番号 R-12-008

最終報告書

フッ化リン酸二ナトリウムのラットを用いる
反復投与毒性・生殖発生毒性併合試験

厚生労働省医薬食品局審査管理課 化学物質安全対策室 委託

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試験番号	R-12-008
被験物質	フッ化リン酸二ナトリウム
試験項目	反復投与毒性ならびに生殖発生毒性試験
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試験終了日	試験責任者の捺印日
試資料保管場所	秦野研究所資料保存室
被験物質保管場所	秦野研究所被験物質保存庫
保管期間	試験終了後 10 年間 その後の保管については試験委託者と協議する。
運営管理者	一般財団法人食品薬品安全センター 秦野研究所 所長 [redacted]

本試験は、「新規化学物質等に係る試験の方法について」(平成 23 年 3 月 31 日付け、薬食発 0331 第 7 号厚生労働省医薬食品局長、平成 23・03・29 製局第 5 号経済産業省製造産業局長、環保企発第 110331009 号環境省総合環境政策局長通知)に準拠し、「新規化学物質等に係る試験を実施する試験施設に関する基準」(平成 23 年 3 月 31 日付け、薬食発 0331 第 8 号厚生労働省医薬食品局長、平成 23・03・29 製局第 6 号経済産業省製造産業局長、環保企発第 110331010 号環境省総合環境政策局長通知)を遵守して実施した。

2014 年 2 月 3 日　　試験責任者 [redacted]

試験従事者

試験責任者	[redacted]
試験担当主任者	
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血液生化学検査	
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信頼性保証書

要約

フッ化リン酸二ナトリウムの反復投与毒性ならびに生殖発生毒性試験を化審法ガイドラインに従って実施した。被験物質を日局注射用水に溶解して、0、15、50 ならびに 150 mg/kg の用量で、各群とも雌雄各 12 匹の Crl:CD(SD)ラットに強制経口投与した。なお、投与 25 日までに 150 mg/kg 群の雄 1 例、雌 3 例が死亡したことから、投与 26 日から 150 mg/kg 群の投与量は 75 mg/kg(以下、150/75 mg/kg 群)に変更した。雄は 42 日間投与した後に剖検し、雌は交配前 2 週間および交配期間、妊娠期間を通して哺育 4 日まで 42～55 日間投与し、出生児は哺育 4 日、母動物は哺育 5 日に剖検した。また、0 および 150/75 mg/kg の用量に非交配雌(10 匹/群)を設け、42 日間投与した後に半数を剖検し、残りの半数と 0 および 150/75 mg/kg 群の雄 5 匹は、投与終了後に 14 日間飼育して剖検した。

1. 反復投与毒性および回復性

150/75 mg/kg 群の雄 1 例と交配雌 1 例および非交配雌 4 例が死亡した。これら死亡例では、立毛、半眼、排便量の減少、被毛の汚れ、耳介の発赤、腹臥位、痩せなどが観察された。死亡例の病理組織学検査では鉱質沈着を伴うびまん性の心筋の変性/壊死がみられた他、腺胃の平滑筋/粘膜下織、腎臓の尿細管および子宮の筋層などにも鉱質沈着を伴う変性/壊死がみられ、大腿骨の骨端/成長板/骨幹端に好塩基性物質の沈着が認められた。生存例では、自発運動の低下が交配雌 1 例、立毛、鼻周囲の汚れ、半眼などが非交配雌 2 例に観察された。尿検査では、尿量の増加が 150/75 mg/kg 群の非交配雌でみられた。血液生化学検査では、50 mg/kg 以上の群の雄に総蛋白濃度の低下、150/75 mg/kg 群の分娩雌に AST と ALP の上昇、さらに 150/75 mg/kg 群の非交配雌に総コレステロールと ALP の上昇がみられた。剖検では、切歯の白濁が 150/75 mg/kg 群の雌雄に観察された。生存例の病理組織学検査では、50 mg/kg 以上の群の雌雄において腺胃の粘膜筋板および粘膜下織に好酸球浸潤と境界縁に樹状細胞様の細胞増加が観察され、150/75 mg/kg 群の雌雄において大腿骨の骨端、成長板および骨幹端に好塩基性物質の沈着がみられた。

回復期間中には、150/75 mg/kg 群で雌雄に体重の減少、雄に尿量の減少が観察され、血液学検査では、雄に MCV の増加がみられた。回復終了時の剖検では 150/75 mg/kg 群の雌雄で切歯の欠落または不正咬合が観察された。150/75 mg/kg 群の病理組織学検査では、びまん性の心筋の線維化が雌 1 例で観察されたが、腺胃および大腿骨の病理組織所見は軽減される傾向にあった。

2. 生殖発生毒性

親動物の性周期、交尾率、妊娠率、妊娠期間、出産率、分娩状態、哺育状態、黄体数、着床数および着床率、出生児の生存率、性比、体重および形態に被験物質の影響を示唆する変化はなかった。

3. 無毒性量

50 mg/kg 群の雄に総蛋白濃度の低下、50 mg/kg 群の雌雄に腺胃の粘膜筋板および粘膜下織に好酸球浸潤と境界縁に樹状細胞様の細胞増加が認められたことから、雌雄動物に対する無毒性量(NOAEL)は 15 mg/kg/day と判断された。150/75 mg/kg 群の親動物ならびに新生児に生殖発生毒性を示唆する変化が認められなかったことから、生殖発生毒性に対する無毒性量は 75 mg/kg/day と判断された。

試験目的

雌雄ラットの交配前(2 週間)および交配期間中(最長 2 週間)、ならびに雄では交配期間終了後 2 週間、雌では妊娠期間を通して周産期(哺育 4 日まで)にフッ化リン酸二ナトリウムを経口投与し、雌雄ラットに対する反復投与毒性および回復性、ならびに生殖発生毒性および新生児の発育に及ぼす影響について検討した。

試験ガイドラインと GLP

本試験は、「新規化学物質等に係る試験の方法について:以下、化審法ガイドライン」(平成 23 年 3 月 31 日付け、薬食発 0331 第 7 号厚生労働省医薬食品局長、平成 23・03・29 製局第 5 号経済産業省製造産業局長、環保企発第 110331009 号環境省総合環境政策局長通知)に準拠し、「新規化学物質等に係る試験を実施する試験施設に関する基準」(平成 23 年 3 月 31 日付け、薬食発 0331 第 8 号厚生労働省医薬食品局長、平成 23・03・29 製局第 6 号経済産業省製造産業局長、環保企発第 110331010 号環境省総合環境政策局長通知)を遵守して実施した。

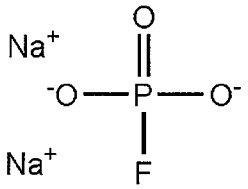
動物愛護

全ての実験操作は、「動物の愛護及び管理に関する法律」(昭和 48 年 10 月 1 日 法律第 105 号、平成 24 年 9 月 5 日 一部改正)、「実験動物の飼養及び保管並びに苦痛の軽減に関する基準」(平成 18 年 4 月 28 日、環境省告示第 88 号)および「厚生労働省の所管する実施機関における動物実験等の実施に関する基本指針」(平成 18 年 6 月 1 日、科発第 0601001 号)を遵守し、「財団法人食品薬品安全センター秦野研究所動物実験に関する指針」(平成 2 年 10 月 1 日、平成 22 年 10 月 1 日改正)に基づいて実施した。本試験における動物実験計画は、秦野研究所動物実験委員会の審査を受け、承認されている(動物実験承認番号:1120218A)。なお、承認された動物実験計画からの変更はなかった。

材料と方法

1. 被験物質

被験物質であるフッ化リン酸二ナトリウム(別名:フルオリドりん酸ジナトリウム、CAS No. 10163-15-2、化学式: FNa_2O_3P、分子量:143.95、性状:白色の粉末、融点:625℃、ロット番号:MKBJ1508V、含量:97.3%、Annex A、以下、SF)は、SIGMA-ALDRICH より購入し(被験物質入手:2012 年 7 月 6 日)、使用時まで冷蔵(実測値 3～7℃)、密閉で保管した。SF の構造式を次に示す。



被験物質の安定性は、実験開始前および実験終了後に秦野研究所にて赤外吸収スペクトルを測定し、スペクトルに変化がなかったことが確認されている(試験番号:G-12-008)。

2. 動物および飼育方法

日本チャールス・リバー厚木飼育センターより 8 週齢の Sprague-Dawley(SD)系〔Crl:CD(SD)、SPF〕ラット雄 55 匹、雌 83 匹を購入し、飼育室(3 号室)に収容した。入荷日も含めて 14 日間、検疫と飼育環境への馴化のため飼育した。その間毎日、動物の一般状態を観察し、入荷日(検疫 1 日)および検疫終了日に体重を測定した。検疫・馴化期間中は動物の尾に赤のフェルトペンで馴化番号を記し、飼育ケージに試験番号、性別および馴化番号を記入した動物カードを掛けて識別した。また、雌動物については、検疫 2 日から毎日、性周期を観察した。入荷動物の入荷時および検疫終了時の体重は下記の通りであった。

動物入荷日	:2012 年 10 月 22 日
入荷時体重	:雄 238.5～277.8 g、雌 176.8～207.9 g
検疫終了日	:2012 年 11 月 4 日
検疫終了時体重	:雄 326.5～417.1 g、雌 204.8～296.9 g

検疫・馴化期間中、雄動物の 1 例(馴化番号 6)で精巣の小型化が確認され、群分け対象から除外した。その他の動物に検疫期間中の一般状態および体重増加の異常は認められず、詳細な症状観察の結果にも試験実施に影響を及ぼすと判断される異常は認められなかった。なお、雌動物については、規則的な性周期の回帰が認められない 7 匹を除外し、検疫終了時の体重に基づく体重別層化無作為抽出法により群分けを行った。群分けした動物には一連の動物番号を割り当て、フェルトペンで尾に動物番号を標識し、色彩の異なった動物カードに試験番号および動物番号を記入して飼育ケージに掛けた。群分けから棄却した雄動物 7 匹、雌動物 15 匹(性周期の結果により除外した例を含む)は全て余剰動物とし、他の目的に転用予定がなかったため、安楽死させた。

動物は許容温度 21.0～25.0℃、許容湿度 40.0～75.0%、換気設定約 15 回/時間、明暗サイクル 12 時間(7 時～19 時)点灯、12 時間(19 時～7 時)消灯に設定された飼育室内で、金属製金網床ケージ(220w×270d×190h mm)に 1 匹ずつ(交配時は 2 匹)収容し、固型飼料(CE-2、日本クレア)と水道水(秦野市水道局給水)を自由に摂取させて飼育した(解剖前の絶食に関しては剖検の項を参照)。雌動物は分娩例全例について、妊娠 18 日から哺育 4 日までラット用プラスチック製繁殖ケージ(350w×400d×180h mm)に 1 匹ずつ収容し、床敷として紙パルプ製チップ(ペパークリーン、日本エスエルシー)を適宜供給した。飼育期間中の動物室の温度は 21.5～24.5℃、湿度は 48.5～75.5%であった。なお、動

物入荷の翌日(2012 年 10 月 23 日 10:30～10:45)に湿式清掃が原因と考えられる湿度の上昇(最高湿度 75.5%)があったが、動物の一般状態に変化は認められず、湿度上昇は短時間であったことから、試験への影響はないと判断した。供給した飼料、飲料水および床敷の分析結果は、いずれも標準操作手順書に記載の許容範囲内であることを確認した。

3. 投与検体

1)調製

被験物質を秤量し、媒体(日局注射用水、製造元:光製薬、製造番号:C23VS1)を加え溶解させ、3 w/v%液を調製した。さらに 3 w/v%液を媒体によって希釈し、1 ならびに 0.3 w/v%液を段階的に調製した。なお、投与 26 日から高用量群に用いる投与検体の濃度を 3 w/v%から 1.5 w/v%に変更したため、1.5 w/v%液は被験物質を秤量し、媒体を加え溶解させ調製した。調製した検体は冷蔵(実測値 2～6℃)・遮光下で保管し、安定性の保証期間内に使用した。

2)安定性試験

日局注射用水を媒体とした 0.02 および 100 mg/mL(0.002 および 10 w/v%)濃度の被験物質調製液については、冷蔵、遮光条件下における 8 日間の安定性が確認されている(試験番号:G-12-008)。

3)含量試験

初回に調製した投与検体(0.3、1、3 w/v%および 1.5 w/v%)について、被験物質含量を測定した。その結果、平均含量は調製濃度の 99.5～103.9 %であり、各測定値のばらつきはそれぞれ平均値の 99.2～100.5 %で規定範囲内にあった(Annex B-1、B-2)。調製検体中の被験物質含量測定は Annex C、第 2 項に従った。

4. 投与量の設定および投与方法

本試験の投与量は、本被験物質を用いて行った「フッ化リン酸二ナトリウムのラットを用いる反復投与毒性・生殖発生毒性併合試験(予備試験)」(試験番号:R-12-007)の結果をもとに設定した。なお、予備試験で使用した被験物質および媒体は本試験と同じロットを用いた。

予備試験では、0(媒体、注射用水)、30、100 および 300 mg/kg の SF を 8 週齢の雌雄各 3 匹の SD 系ラットに 14 日間、反復強制経口投与した結果、300 mg/kg 群の雌雄は、投与 4～7 日の間に全例が死亡した。死亡例の剖検では、雌雄とも心臓に退色域が観察された他、肝臓、肺および胸腺の暗赤色化、前胃粘膜の肥厚、腺胃粘膜の暗赤色域などが観察された。100 mg/kg 群の雄では、赤血球数、血色素量およびヘマトクリット値の低下と脾臓重量の増加傾向が認められたが、同群の雌および 30 mg/kg 群の雌雄には明らかな毒性変化は観察されなかった。

従って、予備試験で全例が死亡した 300 mg/kg の半量の 150 mg/kg を本試験の最高用量に設定し、中用量には長期投与により用量相関性が明確になると予想される 50 mg/kg を、最低用量には無毒性量

(NOAEL)が得られると期待される 15 mg/kg を設定した。なお、試験では投与 25 日までに 150 mg/kg 群の雄 1 例、雌 3 例が死亡したことから、投与 26 日から 150 mg/kg 群の投与量は 75 mg/kg(以下、150/75 mg/kg 群)に変更した。

本試験では、雄動物は交配前 2 週間、交配期間を通して剖検前日まで(総投与回数 42 回)、雌動物は交配前 2 週間、交配期間、妊娠期間を通して分娩後の哺育 4 日まで(総投与回数 42～55 回)、交尾が確認されなかった雌は剖検前日(総投与回数 52 回)、非交配雌の反復毒性を評価するために設定したサテライト群は投与 42 日まで、1 日 1 回、1 週 7 回、毎日 9 時～13 時の間(9 時 06 分～12 時 20 分)に投与した。投与容量は 5 mL/kg とし、雌雄とも最新の測定日の体重を基に投与液量を算出した。なお、対照群には媒体である日局注射用水を同様に投与した。投与経路は化審法ガイドラインに拠り、ラット用胃管による強制経口投与とした。

本試験の群構成および動物番号を以下に示した。

群	投与物質	投与量 (mg/kg)	濃度 (w/v%)	投与容量 (mL/kg)	動物番号	
					雄	雌
対照群	日局注射用水(媒体)	0	0	5	M01001～M01012*	F01001～F01012
低用量群	SF	15	0.3	5	M02013～M02024	F02013～F02024
中用量群	SF	50	1	5	M03025～M03036	F03025～F03036
高用量群	SF	150/75#	3/1.5#	5	M04037～M04048*	F04037～F04048
対照群(サテライト群)	日局注射用水(媒体)	0	0	5	-	F05049～F05058*
高用量群(サテライト群)	SF	150/75#	3/1.5#	5	-	F06059～F06068*

#:投与 26 日から投与量を 150 mg/kg から 75 mg/kg、濃度を 3 w/v%から 1.5 w/v%に変更した。

*:雄の対照群および高用量群と雌の対照群(サテライト群)については動物番号の大きい 5 例を、雌の高用量群(サテライト群)については動物番号の大きい 3 例を回復観察に供した。

5. 検査法

1)親動物(F_0)

①一般状態の観察

全例について、飼育期間中は毎日 1 回、投与期間中は投与前後の毎日 2 回以上観察した。症状が発現した場合、速やかな回復が期待されない所見を除き、症状が発現している間、断続的に、可能な限り観察を継続した。

②回復および遅発毒性の観察

雄動物は対照群および高用量群のうち動物番号の大きい各 5 例を、雌動物はサテライト群の動物番号の大きい 5 例(高用量群は 3 例)を最終投与翌日(回復 1 日)から 14 日間、毎日 1 回以上、一般状態を観察した。

③詳細な症状観察

全例について、検疫終了日、投与 8、15、24、30、36 および 42 日(分娩例は哺育 0 日から 4 日の間)、未交尾例は投与 49 日にも、回復期間中は回復 7 および 14 日にスコアリング法による詳細な症状観察を行った。観察は、いずれも 13 時～17 時の間(13 時 12 分～15 時 41 分)に行った。

まず、ケージ越しでの観察を行い、ケージから取り出す際に外表を観察し、作業台上での観察を行った。作業台上では、体位、姿勢、探索行動、立毛、眼裂、振戦、痙攣、呼吸数、歩行、常同行動、奇妙な行動、挙尾反応、身づくろい、発声、排尿、排便、接触に対する反応、撤去反射、耳介反射を観察した。

④機能検査

各群の動物番号の若い雄 5 例とサテライト群の動物番号の若い 5 例(高用量群は 3 例)については、投与 39 日に自発運動測定と握力測定を実施し、投与 42 日に詳細な症状観察に引き続いて刺激に対する感覚運動反応を検査した。分娩例については投与期間が近接し、出来るだけ分娩から日数が経過した各群の 5 例を選び、投与最終週に自発運動測定、握力測定および刺激に対する感覚運動反応を検査した。

(1) 刺激に対する感覚運動反応

プライエル反応、瞳孔反射、視覚定位、驚愕反応、後肢引込み反射、眼瞼(瞬目)反射、正向反射の有無を検査した。

(2) 握力測定

小動物握力測定システムを用いて握力を測定した。各動物の前肢および後肢の握力をそれぞれ 5 回測定し、最高値および最低値を除外した 3 回の握力値の平均値を求めた。

(3) 自発運動測定

自発運動量測定装置(SUPER-MEX、室町機械)を用いて、20 分間の自発運動量(区画移動数および立ち上がり回数)を計測し、計測値は 5 分毎に集計した。試験対象動物は、検査直前に別室の装置設置場所に運搬し、速やかに自発運動測定を開始した。

⑤体重測定

雄および雌動物のサテライト群は、投与 1(投与開始日)、4、7、14、21、28、35、42 日、回復 1、7、14 日および剖検日に測定した。雌動物は投与 1、4、7、14 日、妊娠 0、7、14、20 日、哺育 0、4 日および剖検日に測定し、未交尾例は投与 21、28、35、42、49 日および剖検日に測定した。

⑥摂餌量測定

雄および雌動物のサテライト群は、投与 1～2、7～8、14～15、29～30、35～36、41～42 日、回復 6～7、12～13 日に測定し、サテライト群は投与 21～22 日にも測定した。雌動物は投与 1～2、7～8、14～15 日および妊娠 0～1、7～8、14～15、20～21 日ならびに哺育 3～4 日に測定し、未交尾例は投与 29～30、35～36、41～42、48～49 日に測定した。

⑦尿検査

雌動物のサテライト群と雄動物を検査対象とし、投与 37 日の検査では各群 5 例、また、回復 13 日における検査では回復例全例を検査した。

投与 37 日の検査では当日の投与後に、回復 13 日の検査では一般状態の観察終了後に動物を代謝ケージに収容し、以下の項目について検査した。ただし、色調・濁度、試験紙による検査および尿沈渣は、採尿開始後約 4～8 時間の時点で採取した蓄尿で、その他の項目は約 24 時間の蓄尿で行った。

項目	測定法	使用機器
色調・濁度	視診	
pH・潜血・蛋白・糖・ケトン体	試験紙法	オーションイレブンAE-4020(アークレイ)
ウロビリノーゲン・ビリルビン	同上	同上
沈渣	鏡検	光学顕微鏡
尿量	計量	メスシリンダー等
比重	屈折法	デジタル臨床屈折計SU-202(エルマ販売)
ナトリウムイオン濃度	イオン電極法	全自動電解質分析装置EA05(エイアンドティー)
カリウムイオン濃度	同上	同上
塩素イオン濃度	同上	同上

⑧性周期観察

全例の雌について、検疫 2 日から性周期を観察し、群分け後、投与開始以降も引き続きサテライト群を除く全例の腟スメア標本を作製し、各動物の同居後、交尾が確認されるまで性周期を観察した。また、群ごとの平均発情回帰日数(個体ごとの発情期から発情期までの日数の平均)および投与開始後に 4 あるいは 5 日間隔の性周期がそれ以外の性周期に変化した動物の頻度を群毎に算出した。なお、規則的に 4～5 日の間隔で性周期が回帰している動物は正常と判断した。

⑨交配

投与 15 日の 16 時 34 分より同群内の雌雄を 1 対 1 で同居させた。なお、高用量群の雄 1 例(動物番号 M04046)が死亡したため、同群の雌 1 例(動物番号 F04046)は投与 18 日の 16 時 29 分より交尾が確認された雄動物(動物番号 M04037)と同居させた。翌朝より毎朝、腟栓を確認し、同居中の雌の腟スメア標本を作製して鏡検した。腟内に腟栓あるいは腟スメア標本中に精子が確認された動物を交尾成立動物とし、この日を妊娠 0 日と起算して個別飼育に戻した。交配結果および妊娠の成否により、同居開始日から交尾確認日までの日数およびその間に回帰した発情期の回数、交尾率〔(交尾動物数/交配に用いた動物数)×100, %〕、妊娠率〔(妊娠動物数/交尾した雌動物数)×100, %〕を算出した。

⑩妊娠・分娩・哺育状態の観察

交尾雌は全例を自然分娩させた。分娩の確認は、妊娠 21 日相当日から分娩が確認されるまで毎日、午前と午後に行い、15 時までに分娩が完了した例について、その日を哺育 0 日(分娩日)とした。分娩状態の直接観察は観察可能な動物について行い、直接観察できなかった動物についても、分娩後の一般状態および産児の状態から異常の有無を判断した。分娩後は、哺育状態を哺育 1～4 日の間、毎日観察した。分娩例については、妊娠期間(妊娠 0 日から分娩日までの日数)を求めた。また、剖検時には、妊娠黄体数と着床数を数え、着床率〔(着床数/妊娠黄体数)×100, %〕を算出した。

⑪採血

雄の投与終了時剖検では各群の動物番号が若い 5 例、回復 15 日における剖検では回復例全例について採血を行った。また、分娩雌の投与終了時剖検では、投与期間が近接した各群の 5 例について

採血を行った。サテライト群の投与終了時剖検では各群の動物番号が若い 5 例(高用量群は 3 例)、回復 15 日における剖検では回復観察に供した全例について採血を行った。いずれも解剖前 18～24 時間絶食させた後、腹部後大静脈から以下の(1)、(2)、(3)の順に注射筒を換えて採血した。

(1) 血液学検査用:抗凝固剤 EDTA-2K

(2) 血液学検査用:抗凝固剤 クエン酸ナトリウム

(3) 血液生化学検査用:抗凝固剤 ヘパリン

⑫血液学検査

採血対象動物について以下の項目を検査した。抗凝固剤としてクエン酸ナトリウムを用いて採取した血液から血漿を分離して、プロトロンビン時間および活性化部分トロンボプラスチン時間を測定し、その他の項目は抗凝固剤として EDTA-2K を用いて採取した血液で測定した。

項目	測定法	使用機器
赤血球数(RBC)	電気抵抗検出法	血液自動分析装置 XT-2000iV(ｼｽﾒｯｸｽ)
白血球数(WBC)	半導体レーザを用いたフローサイトメトリー法	同上
白血球分類	同上	同上
網状赤血球比率(RET%)	同上	同上
血色素量(HGB)	SLS ヘモグロビン法	同上
平均赤血球容積(MCV)	計算(HCT×1000/RBC)	同上
血小板数(PLT)	電気抵抗検出法	同上
ﾍﾏﾄｸﾘｯﾄ値(HCT)	同上	同上
平均赤血球血色素量 (MCH)	計算(HGB×1000/RBC)	同上
平均赤血球血色素濃度 (MCHC)	計算(HGB×100/HCT)	同上
活性化部分ﾄﾛﾝﾎﾞﾌﾟﾗｽﾁﾝ 時間(APTT)	光散乱検出法	全自動血液凝固測定装置 CA-1000(ｼｽﾒｯｸｽ)
ﾌﾟﾛﾄﾛﾝﾋﾞﾝ時間(PT)	同上	同上

⑬血液生化学検査

採血対象動物について以下の項目を検査した。抗凝固剤としてヘパリンを用いて採取した血液から血漿を分離して測定した。なお、得られた血漿の一部は甲状腺機能に関するホルモン(T3、T4 および TSH)測定用として凍結保存(-70℃以下)したが、甲状腺の病理学検査およびその他全ての検査項目の結果から、本被験物質は甲状腺の機能に影響を及ぼさないと判断されたため、甲状腺ホルモンの測定は実施しなかった。

項目	測定法	使用機器
総蛋白濃度(TP)	ﾋﾞｳﾚｯﾄ法	自動分析装置 JCA-BM6010(日本電子)
ｱﾙﾌﾞﾐﾝ濃度(rALB)	BCG 法	同上
ｸﾞﾙｺｰｽ濃度(Glc)	ﾍｷｿｷﾅｰｾﾞ・G-6-PDH 法	同上
総ｺﾚｽﾃﾛｰﾙ濃度(TC)	ｺﾚｽﾃﾛｰﾙｵｷｼﾀﾞｰｾﾞ・HMMPS 法	同上
ﾄﾘｸﾞﾘｾﾗｲﾄﾞ濃度(TG)	GPO・HMMPS 法、ｸﾞﾘｾﾘﾝ消去法	同上
ﾘﾝ脂質濃度(PL)	ｺﾘﾝｵｷｼﾀﾞｰｾﾞ・DAOS 法	同上

項目	測定法	使用機器
尿素窒素濃度(BUN)	ｳﾚｱｰｾﾞ・GℓDH 法,ｳﾚｱｰｾﾞ律速系	自動分析装置 JCA-BM6010(日本電子)
ｸﾚｱﾁﾆﾝ濃度(cre)	Jaffé 法	
γ-ｸﾞﾙﾀﾐﾙﾄﾗﾝｽﾍﾟﾌﾟﾁﾀﾞｰｾﾞ活性(γ-GTP)	IFCC 法	同上
ｱﾙｶﾘﾌｫｽﾌｧﾀｰｾﾞ活性(ALP)	GSCC 法	同上
ｱｽﾊﾟﾗｷﾞﾝ酸ｱﾐﾉﾄﾗﾝｽﾌｪﾗｰｾﾞ活性(AST)	IFCC 法	同上
ｱﾗﾆﾝｱﾐﾉﾄﾗﾝｽﾌｪﾗｰｾﾞ活性(ALT)	同上	同上
乳酸脱水素酵素活性(LDH)	JSCC 標準化対応法	同上
ｶﾙｼｳﾑ濃度(Ca)	OCPC 法	同上
総ﾋﾞﾘﾙﾋﾞﾝ濃度(tbil)	酵素法	同上
無機ﾘﾝ濃度(IP)	ﾓﾘﾌﾞﾃﾞﾝ酸直接法	同上
胆汁酸濃度(TBA)	酵素サイクリング法	同上
A/G 比	計算(rALB/(TP- rALB))	同上
ﾅﾄﾘｳﾑｲｵﾝ濃度(Na)	ｲｵﾝ電極法	全自動電解質分析装置 EA05(ｴｲｱﾝﾄﾞﾃｨｰ)
ｶﾘｳﾑｲｵﾝ濃度(K)	同上	同上
塩素ｲｵﾝ濃度(Cl)	同上	同上

⑭剖検および器官重量

以下の時期に、採血対象動物はペントバルビタールナトリウム麻酔下で採血した後、これ以外の動物はペントバルビタールナトリウム麻酔下で放血致死させ、引き続き剖検した。死亡動物は死亡確認日に剖検した。

対象動物	解剖時期	解剖前の絶食
雄		
投与終了時剖検例	投与 42 日の翌日	18～24 時間絶食
回復観察例	回復 15 日	18～24 時間絶食
雌		
分娩例	哺育 4 日の翌日	18～24 時間絶食
交尾が確認されなかった例(未交尾)	投与 52 日の翌日	実施せず
サテライト群(投与終了時剖検例)	投与 42 日の翌日	18～24 時間絶食
サテライト群(回復観察例)	回復 15 日	18～24 時間絶食
死亡動物	死亡確認日	実施せず

死亡動物以外の全例について、脳、甲状腺および上皮小体、胸腺、心臓、肝臓、腎臓、脾臓、副腎、精巣、精巣上体、前立腺(腹側葉)および精嚢(凝固腺を含む)、卵巣、子宮の重量を測定した。また、全例の脳、脊髄、下垂体、眼球(ハーダー腺)、顎下腺および舌下腺、気管、甲状腺および上皮小体、胸腺、心臓、肺および気管支、肝臓、腎臓、脾臓、膵臓、副腎、胃、十二指腸、空腸、回腸、盲腸、結腸、直腸、下顎リンパ節、腸間膜リンパ節、精巣、精巣上体、前立腺、精嚢および凝固腺、卵巣、子宮、膣、膀胱、大腿骨および大腿骨骨髄、骨格筋、坐骨神経、乳腺、および病変部を採取し、保存した。死亡動物以外の肺および気管支は 15 cm 水柱以下の圧力で、気管内に 10%中性緩衝ホルマリン溶液 5 mL 以下を注入し固定してから摘出して同固定液に保存した。精巣および精巣上体はブアン液に固定(長期保

存は 10%中性緩衝ホルマリン溶液)し、その他の器官・組織は 10%中性緩衝ホルマリン溶液に固定した。

なお、未交尾例の器官重量値は評価対象から除外した。

⑮病理組織学検査

剖検した動物のうち、雄の投与終了時剖検例では対照群ならびに高用量群の動物番号が若い各 5 例、サテライト群の投与終了時剖検例では動物番号が若い対照群の 5 例ならびに高用量群の 3 例、分娩雌の投与終了時剖検例では、採血を行った対照群ならびに高用量群の 5 例について、組織学検査対象器官(保存した器官・組織のうち乳腺は除く)のヘマトキシリン・エオジン(HE)標本を作製し、病理組織学検査を実施した。

死亡動物についても同様に、病理組織学検査を実施した。また、剖検時に異常がみられた器官・組織に関しても HE 標本を作製し、病理組織学検査を実施した。

なお、投与期間終了時剖検例の病理組織学検査において、被験物質投与の影響が示唆された器官・組織については、低および中用量群の 5 例と回復観察剖検例の病理組織学検査を実施した。

2)出生児(F_1)

①出生児の観察

哺育 0 日に生存児数および死亡児数を雌雄別に数えて、性別および外表奇形の有無を観察し、分娩率[(産児数/着床痕数)×100, %]、生児出産率[(出産生児数/着床痕数)×100, %]、出産率[(生児出産雌数/妊娠動物数)×100, %]および出生率[(出産生児数/産児数)×100, %]を算出した。また、哺育 0～4 日まで、毎日、一般状態を観察し、生存児数と死亡児数を雌雄別に数え、新生児生存率[(哺育 4 日の生児数/哺育 0 日の生児数)×100, %]を算出した。生存児については、哺育 0 および 4 日に個別の体重を測定し、腹ごとに雌雄別の平均体重を算出するとともに、哺育 0 日および 4 日における性比[(雄生児数/総生児数)×100, %]を算出した。

②剖検

死亡児は外表奇形の有無を観察して剖検し、10%中性緩衝ホルマリン溶液に固定して保存した。生存児は哺育 4 日に外表奇形の有無を観察してセボフルラン吸入麻酔下に放血致死させて剖検し、内部器官の異常の有無を観察した。

6. データの解析法

性周期の変化した動物の頻度、交尾率、受胎率については Fisher の直接確率検定を行った(有意水準:5%)。被験物質投与群の病理組織学検査所見のうち、グレード分けしたデータは Mann-Whitney の U 検定により、また陽性グレードの合計値は Fisher の直接確率の片側検定により対照群との間の有意差検定を行った(有意水準:5%)。

その他のデータは、個体ごとに得られた値あるいは litter ごとの平均値を 1 標本とし、サテライト群内あるいはその他の群内で比較した。その際、解析の対象が 2 群の場合には、まず F 検定を行い、有意差が認められなければ Student's-t 検定を行った。F 検定において有意差が認められた場合は、Aspin-

Welch 検定を行った。解析の対象が 3 群以上の場合は、先ず、Bartlett の方法により各群の分散の一様性について検定(有意水準:5%)を行った。分散が一様であった場合には、一元配置型の分散分析(有意水準:5%)を行い、群間に有意性が認められた場合は、Dunnett 法により多重比較を行った(有意水準:5%)。一方、いずれかの群で分散が 0 となった場合および分散が一様でなかった場合には、Kruskal-Wallis の順位検定(有意水準:5%)を行い、群間に有意性が認められた場合には、Dunnett 型の検定法により多重比較を行った(有意水準:5%)。

予見することができなかった試験の信頼性に影響を及ぼす疑いのある事態及び試験計画書に従わなかったこと

2012 年 10 月 26 日の 10:21～10:37(16 分間)、14:15～14:16(1 分間)および 16:02～16:07(5 分間)に本館電灯用回路が停電し、本館の動物飼育室内の照明が消えた。しかし、いずれの動物の一般状態、性周期等に上述事象に起因したと考えられる変化は認められず、消灯は短時間であったことから、試験への影響はないと判断した。なお、飼育室の温度および湿度の逸脱はなかった。

その他、「予見することができなかった試験の信頼性に影響を及ぼす疑いのある事態及び試験計画書に従わなかったこと」はなかった。

試験成績

1. 親動物

1)一般状態 (Table 1～Table 4, Appendix 1～Appendix 4)

投与期間中の雄では、投与 15 日に 150/75 mg/kg 群の 1 例(動物番号 M04046)が死亡した。死亡動物では、投与 15 日に自発運動の低下と痩せが観察された。その他、投与 24～35 日に 15 mg/kg 群の 1 例(動物番号 M02018)で痂皮形成がみられた。

回復期間中の雄では、回復 15 日に 150/75 mg/kg 群の 1 例(動物番号 M04047)で歯の欠損がみられた。

投与期間中の雌では、投与 21 日から 28 日の間に 150/75 mg/kg 群の交配雌 1 例(動物番号 F04046)および非交配雌 4 例(動物番号 F06060、F06061、F06062、F06063)が死亡した。これら死亡動物では、立毛、半眼、排便量の減少、被毛の汚れ、耳介の発赤、腹臥位、痩せなどが観察された(次表参照)。

動物番号	剖検日(死亡日)	死亡までの症状
交配雌		
F04046	妊娠 7 日相当日 (投与 26 日)	立毛、半眼、排便量の減少、口の周囲の汚れ、うずくまり、痩せ(妊娠 4～6 日相当日)。
非交配雌		
F06060	投与 25 日	鼻の周囲の汚れ、耳介の発赤、立毛、排便量の減少、痩せ、体温下降(投与 23～24 日)。
F06061	投与 22 日	腹臥位、耳介の発赤、痩せ(投与 20～21 日)。
F06062	投与 28 日	立毛、腹臥位、被毛の汚れ、半眼(投与 27 日)。
F06063	投与 21 日	痙攣、立毛、半眼、痩せ、チアノーゼ(投与 20 日)。

150/75 mg/kg 群の生存雌においても、哺育 1 日に自発運動の低下が交配雌 1 例(動物番号 F04040)、投与 22～24 日に立毛、鼻周囲の汚れ、半眼、排便量の減少、耳介の発赤およびうずくまりが非交配雌 1 例(動物番号 F06066)、投与 24 日に立毛が非交配雌 1 例(動物番号 F06065)に観察された。その他、投与 40～42 日に紅涙が 150/75 mg/kg 群の非交配雌 1 例(動物番号 F06067)に観察された。50 mg/kg 以下の群では、異常は認められなかった。

回復期間中の非交配雌では、紅涙が 150/75 mg/kg 群の 2 例(動物番号 F06067、F06068)に観察された以外に、異常は認められなかった。

2)詳細な症状観察 (Table 5～Table 6, Appendix 5～Appendix 6)

詳細な症状観察では、雌雄とも投与期間ならびに回復期間を通して、被験物質投与の影響を示唆する変化は認められなかった。

3)体重 (Table 7～Table 10, Appendix 7～Appendix 10)

投与期間中の雄では、体重推移に被験物質投与の影響を示唆する変化は認められなかった。

回復期間中の雄では、150/75 mg/kg 群の回復 14 日の体重が減少したが、対照群と比較して有意差は認められなかった。

投与期間中の非交配雌を含む雌では、体重推移に被験物質投与の影響を示唆する変化は認められなかった。

回復期間中の非交配雌では、150/75 mg/kg 群の回復 14 日の体重が回復 7 日より減少したが、対照群と比較して有意差は認められなかった。

妊娠および哺育期間中の雌では、体重推移に被験物質投与の影響を示唆する変化は認められなかった。

4)摂餌量 (Table 11～Table 14, Appendix 11～Appendix 14)

投与期間中の雄では、摂餌量に被験物質投与の影響を示唆する変化は認められなかった。

回復期間中の雄では、150/75 mg/kg 群の摂餌量が対照群より低値を示したが、有意差はなかった。

投与期間中の非交配雌を含む雌では、摂餌量に被験物質投与の影響を示唆する変化は認められなかった。

回復期間中の非交配雌では、摂餌量に被験物質投与の影響を示唆する変化は認められなかった。

妊娠および哺育期間中の雌では、摂餌量に被験物質投与の影響を示唆する変化は認められなかった。

5)機能検査

①刺激に対する感覚運動反応 (Table 15～Table 16, Appendix 15～Appendix 16)

投与最終週に実施したプライエル反応、瞳孔反射、視覚定位、驚愕反応、後肢引込み反射、眼瞼反射、正向反射の検査では、非交配雌を含む雌雄いずれの群の検査対象動物においても異常は認められなかった。

②握力測定 (Table 17～Table 19, Appendix 17～Appendix 19)

投与最終週に実施した前肢および後肢の握力測定では、非交配雌を含む雌雄とも、被験物質投与の影響を示唆する変化は認められなかった。

③自発運動量測定 (Table 20～Table 22, Appendix 20～Appendix 22)

投与期間中の雄では、区画移動数および立ち上がり回数に被験物質の影響を示唆する変化は認められなかった。

投与期間中の分娩雌では、150/75 mg/kg 群の開始 5 分の区画移動数(平均 1249 counts)、50 mg/kg 群の総区画移動数(平均 3286 counts)および 150/75 mg/kg 群の総区画移動数(平均 3415 counts)が対照群と比較して有意に増加したが、150/75 mg/kg 群の 1 例(動物番号 F042042)以外は、いずれの個体も背景データの範囲(下表参照)内の値を示したことから、偶発的な変化と判断した。なお、150/75 mg/kg 群の 1 例(動物番号 F042042)に哺育状態の異常は観察されなかった。

投与期間中の非交配雌では、150/75 mg/kg 群の区画移動数および立ち上がり回数に対照群との差は認められなかった。

分娩雌(投与終了時)	試験数*	サンプル数	平均	平均±2SD
開始 5 分の区画移動数	4	20	1115	791-1438
総区画移動数	4	20	3068	1345-4791

*: 2011 年 4 月～2013 年 3 月に実施した併合試験の媒体対照群(媒体:注射用水)を使用

6)尿検査 (Table 23～Table 24, Appendix 23～Appendix 24)

投与期間中の雄では、被験物質投与の影響を示唆する尿の変化は観察されなかった。

回復期間中の雄では、150/75 mg/kg 群の尿量が対照群と比較して有意に減少し、尿量の減少に伴う変化と考えられる塩素イオン濃度とナトリウムイオン、カリウムイオンおよび塩素イオン排泄量の有意な減少がみられた。

投与期間中の非交配雌では、150/75 mg/kg 群の尿量が対照群と比較して有意に増加し、尿量の増加に伴う変化と考えられる尿比重、ナトリウムイオン濃度、カリウムイオン濃度および塩素イオン濃度の有

意な減少がみられた。

回復期間中の非交配雌では、被験物質投与の影響を示唆する尿の変化は観察されなかった。

7)血液学検査 (Table 25～Table 26, Appendix 25～Appendix 26)

①雄動物

投与期間終了時の雄では、被験物質投与の影響を示唆する変化は観察されなかった。

回復期間終了時の雄では、150/75 mg/kg 群のヘマトクリット値(平均 43.1%)と MCV(平均 55.1 fL)が対照群と比較して有意に増加し、MCHC(平均 33.1 g/dL)が有意に低下した。各個体のヘマトクリット値および MCHC はいずれも背景データの範囲(下表参照)内あるいはわずかに外れる程度の変化であったが、MCV については、5 例中 4 例が背景データの範囲を上回った。その他の項目には、被験物質投与の影響を示唆する変化は認められなかった。

雄(回復終了時)	試験数*	サンプル数	平均	平均±2SD
ヘマトクリット値	4	20	42.0	38.9-45.0
MCV	4	20	50.9	47.9-53.8
MCHC	4	20	34.7	32.9-36.5

*: 2011 年 4 月～2013 年 3 月に実施した併合試験の媒体対照群(媒体:注射用水)を使用

②雌動物

投与期間終了時の分娩雌では、被験物質投与の影響を示唆する変化は観察されなかった。

投与期間終了時の非交配雌では、150/75 mg/kg 群の MCV(平均 54.6 fL)と MCH(19.2 pg)が対照群と比較して有意に増加したが、いずれも背景データの範囲(下表参照)内あるいはわずかに上回る程度の変化であり、被験物質の影響でないと判断した。その他の項目に被験物質投与の影響を示唆する変化は認められなかった。

非交配雌(投与終了時)	試験数*	サンプル数	平均	平均±2SD
MCV	4	20	53.1	51.3-54.9
MCH	4	20	18.8	18.6-19.0

*: 2011 年 4 月～2013 年 3 月に実施した併合試験の媒体対照群(媒体:注射用水)を使用

回復期間終了時の非交配雌では、150/75 mg/kg 群の活性化部分トロンボプラスチン時間が対照群と比較して有意に短縮したが、延長の変化ではないことから影響ではないと判断した。その他の項目に被験物質投与の影響を示唆する変化は認められなかった。

8) 血液生化学検査 (Table 27～Table 28, Appendix 27～Appendix 28)

①雄動物

投与期間終了時の雄では、総蛋白濃度が 50 mg/kg 群(平均 5.2 g/dL)および 150/75 mg/kg 群(平均 5.3 g/dL)で対照群と比較して有意に低下し、これらの値はいずれも背景データの範囲(下表参照)をわずかに下回った。

雄(投与終了時)	試験数*	サンプル数	平均	平均±2SD
総蛋白濃度	4	20	5.7	5.4-5.9

*: 2011 年 4 月～2013 年 3 月に実施した併合試験の媒体対照群(媒体:注射用水)を使用

回復期間終了時の雄では、被験物質投与の影響を示唆する変化は認められなかった。

②雌動物

投与期間終了時の分娩雌では、150/75 mg/kg 群の AST(平均 105 U/L)と ALP(平均 242 U/L)が対照群と比較して有意に増加し、これらの値はいずれも背景データの範囲(下表参照)を上回った。

分娩雌(投与終了時)	試験数*	サンプル数	平均	平均±2SD
AST	4	20	84	64-104
ALP	4	20	160	149-171

*: 2011 年 4 月～2013 年 3 月に実施した併合試験の媒体対照群(媒体:注射用水)を使用

投与期間終了時の非交配雌では、150/75 mg/kg 群の総コレステロール(平均 81 mg/dL)と ALP(平均 219 U/L)が対照群と比較して有意に増加し、これらの値は背景データ (下表参照)と比較しても高い値であった。

非交配雌(投与終了時)	試験数*	サンプル数	平均	平均±2SD
総コレルテロール	4	20	64	54-73
ALP	4	20	156	84-229

*: 2011 年 4 月～2013 年 3 月に実施した併合試験の媒体対照群(媒体:注射用水)を使用

回復期間終了時の非交配雌では、150/75 mg/kg 群の胆汁酸濃度(平均 16.0 μmol/L)が対照群と比較して有意に増加したが、背景データの範囲(下表参照)内であり、被験物質の影響ではないと判断した。

非交配雌(回復終了時)	試験数*	サンプル数	平均	平均±2SD
胆汁酸濃度	4	20	14.4	1.2-27.6

*: 2011 年 4 月～2013 年 3 月に実施した併合試験の媒体対照群(媒体:注射用水)を使用

9)器官重量 (Table 29～Table 30, Appendix 29～Appendix 30)

①雄動物

投与期間終了時および回復期間終了時の雄では、被験物質投与の影響を示唆する器官重量の変化は観察されなかった。

②雌動物

投与期間終了時の分娩雌では、150/75 mg/kg 群の副腎重量が高値を示し、相対重量が対照群と比較して有意に増加したが、その他の測定器官に被験物質投与の影響を示唆する変化は観察されなかった。

投与期間終了時の非交配雌では、被験物質投与の影響を示唆する器官重量の変化は観察されなかった。

回復期間終了時の非交配雌では、被験物質投与の影響を示唆する器官重量の変化は観察されなかった。

10)剖検所見 (Table 31～Table 32, Appendix 31～Appendix 32)

①雄の死亡動物

途中死亡した 150/75 mg/kg 群の 1 例(動物番号 M04046)の剖検所見は以下の通りである。

胃では腺胃粘膜に暗赤色点が、心臓では白色域がそれぞれ散在し、腎臓では両側性に大型化が認められた。その他、肝臓の暗色化、肺の赤色化、脾臓および胸腺の小型化が観察された。

②雄の投与終了時剖検例

投与 42 日の翌日に剖検した雄動物、対照群 7 例、15 mg/kg 群 12 例、50 mg/kg 群 12 例および 150/75 mg/kg 群 6 例の剖検所見は以下の通りである。

精巣上体では、片側に黄白色結節が 15 mg/kg 群の 1 例に認められたが、同様の所見は対照群の 1 例にもみられた。

腎臓では、片側性の淡色域が 150/75 mg/kg 群の 1 例(動物番号 M04041)、白色域および白色点の散在が 150/75 mg/kg 群の 1 例(動物番号 M04042)に観察されたが、片側性の白色域は対照群の 1 例(動物番号 M01002)にも観察された。

肝臓では、白色斑が 50 mg/kg 群の 1 例(動物番号 M03025)に認められた。

回腸では、憩室が 50 mg/kg 群の 1 例(動物番号 M03029)に認められた。

上切歯では、白濁が 150/75 mg/kg 群の 2 例に観察された。

③雄の回復観察例

回復 15 日に剖検した雄動物、対照群 5 例および 150/75 mg/kg 群 5 例の剖検では、上切歯の欠落あるいは破砕が 150/75 mg/kg 群の 2 例に観察された。

④雌の死亡動物

途中死亡した 150/75 mg/kg 群の交配雌 1 例(動物番号 F04046)および非交配雌 4 例(動物番号 F06060、F06061、F06062、F06063)の剖検所見は以下の通りである。

副腎では、大型化が非交配雌 2 例(動物番号 F06060、F06062)にみられ、うち 1 例(動物番号 F06062)は暗色化を伴っていた。

心臓では、白色域散在が交配雌 1 例(動物番号 F04046)および非交配雌 3 例(動物番号 F06060、F06061、F06062)に認められた。

腎臓では、両側性の淡色化が交配雌および非交配雌の各 1 例(動物番号 F04046、F06061)に認められた。

肝臓では、暗色化が非交配雌 2 例(動物番号 F06061、F06063)に認められた。

脾臓では、小型化が交配雌 1 例(動物番号 F04046)および非交配雌 2 例(動物番号 F06062、F06063)にみられ、うち 1 例(動物番号 F06062)は淡色化を伴っていた。

胸腺では、小型化が交配雌および非交配雌の各 1 例(動物番号 F04046、F06061)に認められた。

⑤分娩雌の投与終了時剖検例

哺育 4 日の翌日に剖検した雌動物、対照群 11 例、15 mg/kg 群 12 例、50 mg/kg 群 12 例、および 150/75 mg/kg 群 11 例の剖検所見は以下の通りである。

腎臓では、白色斑散在が 150/75 mg/kg 群の 1 例に認められた。

肝臓では、横隔膜面の結節が 15 mg/kg 群の 1 例(動物番号 F02021)に認められた。

胸腺では、小型化が 150/75 mg/kg 群の 1 例(動物番号 F04040)に認められた。

切歯では、上切歯または下切歯の白濁が 150/75 mg/kg 群の 2 例に観察された。

⑥未交尾例

交尾が確認されなかった対照群の 1 例(動物番号 F01011)の剖検では、異常は観察されなかった。

⑦サテライト群の投与終了時剖検例

投与 42 日の翌日に剖検した非交配雌、対照群 5 例および 150/75 mg/kg 群 3 例の剖検では、上切歯または下切歯の白濁が 150/75 mg/kg 群の 2 例に観察された。

⑧サテライト群の回復観察例

回復 15 日に剖検した非交配雌、対照群 5 例および 150/75 mg/kg 群 3 例の剖検では、投与 22～24 日に立毛、鼻周囲の汚れなどの症状を示した 150/75 mg/kg 群の 1 例(動物番号F06066)で心臓の淡色化が、他の 1 例(動物番号F06068)で切歯の不正咬合が観察された。

11)病理組織学検査 (Table 33～Table 34, Appendix 33～Appendix 34)

①雄の死亡動物

途中死亡した 150/75 mg/kg 群の 1 例(動物番号 M04046)の病理組織所見は以下の通りである。

下顎リンパ節では、可染体マクロファージの著しい増加がみられた。

胸腺では、軽度の萎縮と可染体マクロファージの中等度の増加がみられた。

心臓では、鉱質沈着を伴うびまん性の心筋変性および壊死が観察されたが、ごく軽度な変化であった。

肝臓では、小葉中心性で軽度な肝細胞の空胞化が認められた。

胃では、腺胃の粘膜筋板および粘膜下織に中等度の好酸球浸潤が認められ、境界縁にごく軽度な樹

状細胞様の細胞が増加していた。

腸間膜リンパ節では、可染体マクロファージの中等度の増加がみられた。

脾臓では、白脾髄の軽度な萎縮が認められた他、中等度の褐色色素沈着や軽度の髄外造血がみられた。

腎臓では、好塩基性を示す集合管に核の大小不同、核異型、分裂像が中等度に観察された他、鉱質沈着を伴った尿細管の軽度な変性および壊死と遠位尿細管の軽度な管腔拡張が認められた。

副腎では、束状帯細胞の肥大が認められたが、ごく軽度な変化であった。

ハーダー腺では、中等度の色素沈着過度が認められた。

大腿骨では、骨端、成長板および骨幹端で中等度に好塩基性物質の沈着がみられた。

②雄の投与終了時剖検例

投与終了時剖検例のうち、採血を行った対照群および 150/75 mg/kg 群の 5 例について病理組織学検査を実施し、さらに被験物質の影響が示唆された心臓、胃、腎臓および大腿骨については、15 および 50 mg/kg 群の 5 例についても病理組織学検査を実施した。その他、剖検時に異常が認められた器官についても病理組織学検査を実施した。病理組織所見は、以下の通りである。

甲状腺では、150/75 mg/kg 群において異所性の胸腺組織が 1 例、鰓後体遺残が 2 例に認められたが、被験物質投与の影響を示唆する変化は認められなかった。

心臓では、心筋の変性/線維化が 15 mg/kg 群の 3 例および 50 mg/kg 群の 2 例に認められたが、いずれも限局性でごく軽度な変化であった。

肺では、限局性でごく軽度の骨化生が 150/75 mg/kg 群の 1 例に認められたのみであった。

肝臓では、150/75 mg/kg 群において門脈周囲性に肝細胞の脂肪化が 2 例、小肉芽腫が 2 例にみられたが、いずれもごく軽度な変化で、対照群と比較して頻度および程度の差はなかった。その他、剖検時に肝臓の異常がみられた 50 mg/kg 群の 1 例(動物番号 M03025)に、門脈周囲性の肝細胞の脂肪化と空胞化細胞巣がみられたが、いずれもごく軽度の変化であった。

膵臓では、ごく軽度な膵管の過形成が 150/75 mg/kg 群の 1 例に認められた。

胃では、腺胃の粘膜下織にごく軽度から軽度のリンパ球集簇が 50 mg/kg 群および 150/75 mg/kg 群の各 3 例に認められた。また、腺胃の粘膜筋板および粘膜下織に好酸球浸潤が対照群を含む全ての動物に認められ、その程度が 50 mg/kg 以上の群で対照群と比較して有意に増加した。その他、対照群を含む全ての投与群で境界縁に樹状細胞様の細胞が増加し、50 mg/kg 以上の群の頻度および程度が対照群に比較して有意に増加した。

回腸では、剖検時に異常が認められた 50 mg/kg 群の 1 例(動物番号 M03029)に憩室が確認された。

脾臓では、褐色色素の沈着と髄外造血が対照群および 150/75 mg/kg 群の全例に認められたが、その程度に群間の差はなかった。

腎臓では、皮質にごく軽度から軽度の好塩基性尿細管が対照群を含む全ての投与群に認められたが、その程度および頻度に群間の差は認められなかった。また、間質にごく軽度から軽度のリンパ球浸潤が 15 および 50 mg/kg 群の各 1 例と 150/75 mg/kg 群の 2 例に認められたが、対照群と比較して頻度およ

び程度の差はなかった。その他、150/75 mg/kg 群において遠位尿細管のごく軽度な管腔内拡張が 1 例、皮質のごく軽度な鉱質沈着が 3 例、腎芽腫が 1 例に認められた他、髄質の嚢胞が対照群と 15 mg/kg 群の各 1 例に観察された。

精巣上体では、剖検時に異常がみられた対照群および 15 mg/kg 群の各 1 例に精子肉芽腫が認められたが、150/75 mg/kg 群で同様の異常は認められなかった。

前立腺では、間質にごく軽度のリンパ球浸潤が 150/75 mg/kg 群の 2 例に認められたが、対照群の 2 例にもみられた変化であった。

大腿骨では、150/75 mg/kg 群の 5 例(全例)において骨端、成長板および骨幹端に中等度の好塩基性物質の沈着が認められ、頻度および程度とも対照群と比較して有意に増加した。50 mg/kg 以下の群においては、同様の沈着物質は観察されなかった。

③雄の回復観察例

回復 15 日に剖検した対照群および 150/75 mg/kg 群の 5 例については、投与終了時の剖検例で被験物質の影響が示唆された心臓、胃、腎臓および大腿骨について病理組織学検査を実施した。病理組織所見は、以下の通りである。

心臓では、心筋の変性/線維化が 150/75 mg/kg 群の 2 例に認められたが、対照群の 1 例にも認められた限局性でごく軽度な変化であった。

胃では、腺胃の粘膜下織にごく軽度のリンパ球集簇が 150/75 mg/kg 群の 1 例に認められた。その他、腺胃の粘膜筋板および粘膜下織に好酸球浸潤が 150/75 mg/kg 群の全ての動物に認められたが、対照群の全例にも認められその程度に対照群との差はなかった。また、150/75 mg/kg 群の 4 例では、境界縁に樹状細胞様の細胞増加がごく軽度または軽度にみられたが、対照群の 1 例にも同様の所見は認められた。

腎臓では、皮質にごく軽度の好塩基性尿細管が 150/75 mg/kg 群の 4 例に認められたが、程度および頻度に対照群と差はなかった。その他、間質にリンパ球浸潤が 150/75 mg/kg 群の 2 例に認められた。

大腿骨では、被験物質投与の影響は認められなかった。

④雌の死亡動物

150/75 mg/kg 群の死亡動物、交配雌 1 例(動物番号 F04046)および非交配雌 4 例(動物番号 F06060、F06061、F06062、F06063)について病理組織学検査を実施した。病理組織所見は、以下の通りである。

下顎リンパ節では、ごく軽度の萎縮が非交配雌 1 例、可染体マクロファージの軽度あるいは中等度の増加が非交配雌 2 例にみられた。

甲状腺では、鰓後体遺残が非交配雌 1 例にみられた。

胸腺では、軽度または中等度の萎縮が交配雌 1 例および非交配雌 2 例にみられた。

心臓では、鉱質沈着を伴うびまん性の心筋変性および壊死が 5 例(全例)に観察され、その内の交配雌 1 例(動物番号 F04046)および非交配雌 3 例(動物番号 F06060、F06061、F06062)の程度は中等度または重度であった(Photo 1)。

肺では、肺胞壁にごく軽度な好中球浸潤が非交配雌 1 例、限局性でごく軽度な骨化生が非交配雌 1 例、また、細動脈に限局性でごく軽度な血栓が非交配雌 2 例に観察された。

肝臓では、肝細胞の好塩基性変化が 5 例(全例)に認められたが、いずれもごく軽度または軽度な変化であった。その他、多巣性で中等度の壊死が非交配雌 1 例に認められた。

胃では、腺胃の粘膜筋板および粘膜下織にごく軽度から中等度の好酸球浸潤が 5 例(全例)に認められ、さらに非交配雌 2 例には粘膜下織および平滑筋に鉱質沈着を伴う中等度の変性および壊死(Photo 2)がみられた。

腸間膜リンパ節では、ごく軽度の萎縮が交配雌 1 例および非交配雌 3 例に、軽度の可染体マクロファージ増加が非交配雌 1 例にみられた。

脾臓では、軽度または中等度の白脾髄の萎縮が交配雌 1 例および非交配雌 3 例、軽度または中等度の赤脾髄のうっ血が非交配雌 3 例、軽度または中等度の褐色色素沈着が 5 例(全例)およびごく軽度の髄外造血が 5 例(全例)にみられた。

腎臓では、好塩基性を示した集合管に軽度または中等度の核の大小不同/核異型/分裂像(Photo 3)が 4 例に観察された他、軽度または中等度の好塩基性を示した直部近位尿細管が 2 例、鉱質沈着を伴ったごく軽度から中等度の尿細管変性および壊死(Photo 4)が交配雌 1 例および非交配雌 3 例、曲部近位尿細管の軽度な空胞変性が交配雌 1 例に認められた。

副腎では、ごく軽度な束状帯細胞の肥大が交配雌 1 例および非交配雌 2 例に認められた。

卵巣では、閉鎖卵胞のごく軽度な増加が非交配雌 1 例に認められた。

子宮では、筋層の空胞変性が非交配雌 3 例、鉱質沈着を伴った筋層の変性および壊死が非交配雌 3 例に認められた。

膣では、粘膜上皮の粘液細胞化が交配雌 1 例に認められた。

ハーダー腺では、中等度の色素沈着過度が非交配雌 4 例に認められた。

大腿骨では、骨端、成長板、骨幹端にごく軽度から中等度で好塩基性物質の沈着が非交配雌 4 例にみられた。

⑤分娩雌の投与終了時剖検例

哺育 4 日の翌日に剖検した雌動物のうち、採血を行った対照群および 150/75 mg/kg 群の各 5 例について病理組織学検査を実施し、さらに被験物質の影響が示唆された心臓、胃、腎臓および大腿骨については、15 および 50 mg/kg 群の 5 例についても病理組織学検査を実施した。その他、剖検時に異常が認められた器官についても病理組織学検査を実施した。病理組織所見は、以下の通りである。

下垂体では、ラトケ嚢遺残が 150/75 mg/kg 群の 1 例に認められた。

舌下腺では、腺房細胞の中等度萎縮および間質に単核細胞浸潤がいずれも片側性に 150/75 mg/kg 群の 1 例で認められたが、その他の動物に舌下線の異常は認められなかった。

甲状腺では、鰓後体遺残が対照群および 150/75 mg/kg 群の各 2 例にみられた。

胸腺では、剖検時に異常がみられた 150/75 mg/kg 群の 1 例(動物番号 F04040)に中等度の萎縮が観察された。

心臓では、動脈周囲に軽度の水腫が 150/75 mg/kg 群の 1 例に観察された。

肝臓では、門脈周囲性にごく軽度な肝細胞の脂肪化が 150/75 mg/kg 群の 1 例に観察されたが、対照群の 1 例にも観察された変化であった。また、限局性の壊死が 150/75 mg/kg 群の 1 例に観察されたが、ごく軽度な変化であった。その他、剖検時に異常がみられた 15 mg/kg 群の 1 例(動物番号 F02021)において限局性の出血を伴う横隔膜ヘルニアがみられ、門脈周囲性に軽度な肝細胞の脂肪化も観察された。

胃では、腺胃の粘膜筋板および粘膜下織に好酸球浸潤が対照群の 3 例と 15、50 および 150/75 mg/kg 群の各 5 例(全例)に認められ、その程度は 50 mg/kg 以上の群で対照群と比較して有意に増加した。また、境界縁に樹状細胞様の細胞増加が 15 mg/kg 以上の群でみられ、50 mg/kg 群の頻度および程度が対照群と比較して有意に増加した。その他、腺胃の粘膜下織にごく軽度なリンパ球の集簇が 150/75 mg/kg 群の 1 例に認められた。

脾臓では、対照群と 150/75 mg/kg 群の全例に褐色色素沈着と髄外造血が観察されたが、その程度に両群間の差はなかった。

腎臓では、皮質の好塩基性尿細管が対照群を含む各群で観察されたが、頻度および程度に差はなかった。また、鉱質沈着を伴った軽度の尿細管変性および壊死と遠位尿細管のごく軽度な管腔拡張が 150/75 mg/kg 群の 1 例に、皮髄境界部または髄質の鉱質沈着が 15、50 および 150/75 mg/kg 群の各 1 例に観察された。その他、50 mg/kg 群の 1 例に好塩基性を示した直部近位尿細管が認められたが、用量に存した変化ではなかった。

大腿骨では、骨端、成長板および骨幹端にごく軽度から中等度の好塩基性物質の沈着が 150/75 mg/kg 群の 5 例(全例)にみられ、頻度、程度とも対照群と比較して有意に増加したが、50 mg/kg 以下の群に同様の変化は認められなかった。

⑥サテライト群の投与終了時剖検例

非交配雌の投与終了時剖検例、対照群 5 例および 150/75 mg/kg 群 3 例の病理組織所見は以下の通りである。

甲状腺では、異所性の胸腺組織が 150/75 mg/kg 群の 1 例にみられた。

胸腺では、ごく軽度または中等度の可染体マクロファージが 150/75 mg/kg 群の 2 例にみられたが、ごく軽度な変化は対照群の 1 例にも観察された。

肺では、肺胞内にごく軽度な泡沫細胞の集簇が 150/75 mg/kg 群の 1 例に認められた。

肝臓では、150/75 mg/kg 群において門脈周囲性にごく軽度な肝細胞の脂肪化が 1 例、ごく軽度の小肉芽腫が 1 例に観察されたが、その頻度および程度に対照群と差はなかった。

胃では、腺胃の粘膜筋板および粘膜下織に好酸球浸潤(Photo 5)が対照群および 150/75 mg/kg 群の全例に認められたが、その程度に群間の差はなかった。また、境界縁に樹状細胞様の細胞増加(Photo 6)が 150/75 mg/kg 群の 3 例にみられ、その程度は対照群と比較して有意に増加した。

脾臓では、対照群と 150/75 mg/kg 群の全例に褐色色素沈着と髄外造血が観察されたが、その程度に両群間の差はなかった。

腎臓では、150/75 mg/kg 群の 2 例に皮質の好塩基性尿細管が観察されたが、その程度および頻度に対照群との差はなかった。

大腿骨では、骨端、成長板、骨幹端に好塩基性物質の軽度な沈着が 150/75 mg/kg 群の 3 例(全例)に認められ、対照群と比較して頻度および程度が有意に増加した(Photo 7)。

⑧サテライト群の回復観察例

回復 15 日に剖検した非交配雌、対照群の 5 例および 150/75 mg/kg 群の 3 例については、投与終了時の剖検例で被験物質の影響が示唆された心臓、胃、腎臓および骨髄について病理組織学検査を実施した。

心臓では、剖検時に心臓の異常がみられた 150/75 mg/kg 群の 1 例(動物番号F06066)にびまん性で中程度の心筋の線維化が観察されたが、同群のその他の動物に異常はみられなかった。

胃では、腺胃の粘膜筋板および粘膜下織に好酸球浸潤が対照群および 150/75 mg/kg 群の全例に認められ、その程度に両群間の差はなかった。また、境界縁に樹状細胞様の細胞増加が 150/75 mg/kg 群の 3 例(全例)にみられたが、その程度および頻度には対照群と比較して有意差はなかった。

腎臓では、150/75 mg/kg 群において皮質の好塩基性尿細管が 1 例、髄質の嚢胞が 1 例、皮髄境界部または髄質の鉱質沈着が 2 例に観察されたが、それらの頻度および程度に対照群と比較して有意差は認められなかった。

大腿骨では、被験物質投与の影響は認められなかった。

2. 生殖能力

1)性周期および交配成績 (Table 35～Table 36, Appendix 35～Appendix 36)

投与開始後に 50 mg/kg 群の 1 例で性周期の異常が観察されたが、同群の交尾率および妊娠率はいずれも 100%であった。その他の群の交尾率、妊娠率、さらには投与期間中の平均発情回帰日数、同居開始日から交尾確認日までの日数およびその間に回帰した発情期の回数に被験物質投与の影響を示唆する変化は認めらなかった。

2)出産率および妊娠期間 (Table 37, Appendix 37)

妊娠期間および出産率に被験物質投与の影響は認められなかった。

3)分娩および哺育状態 (Table 37, Appendix 37)

分娩状態は、いずれの動物も良好であった。また、いずれの動物の哺育状態についても、異常は認められなかった。

4)黄体数、着床数および着床率 (Table 37, Appendix 37)

150/75 mg/kg 群の着床数は対照群と比較して有意に増加したが、黄体数および着床率に被験物質投与の影響は認められなかった。

3. 出生児

1)生存 (Table 37, Appendix 37)

産児数、出産生児数、分娩率、生児出産率、出生率、哺育 0 日および哺育 4 日の性比および新生児生存率に被験物質投与の影響は認められなかった。また、哺育 0 日に産児の外表奇形は観察されなかった。

2)体重 (Table 38, Appendix 38)

哺育 0 日に測定した出生児体重には、雌雄とも被験物質投与の影響を示唆する変化は認められなかった。

哺育 4 日に測定した出生児体重では、50 mg/kg 群の雌の体重が対照群と比較して有意に増加したが、被験物質投与の影響を示唆する変化は認められなかった。

3)出生児観察(Table 39～Table 40, Appendix 39)

出生児の一般状態観察では、被験物質投与の影響を示唆する変化はみられなかった。死亡児の剖検では、15 mg/kg 群の雄 1 例に全身浮腫および鎖肛が認められたが、その他の死亡児に異常は認められず、哺育 4 日の生存児の剖検においても、外表奇形および内部器官の異常は観察されなかった。

考察

雌雄ラットの交配前(2 週間)および交配期間中、ならびに雄では交配期間終了後を通して計 42 日間、雌では妊娠期間を通して周産期(哺育 4 日まで)にフッ化リン酸二ナトリウムを経口投与し、雌雄ラットに対する反復投与毒性および回復性、ならびに生殖発生毒性および新生児の発育に及ぼす影響について検討した。

1. 反復投与毒性

投与 25 日までに 150 mg/kg を投与した雄 1 例、雌 3 例が死亡し、投与量を 75 mg/kg に変更した以降にも雌 2 例が死亡した。投与量設定のための予備試験(試験番号:R-12-007)においても 300 mg/kg 群の雌雄全例が投与 4～7 日の間に死亡していることから、本試験にみられた死亡は、被験物質投与による影響と考えられた。

死亡動物の剖検では心臓に白色域が認められ、心臓の病理組織学検査ではびまん性に心筋の変性および壊死が確認されていることから、これが主な死亡原因と考えられる。なお、15 および 50 mg/kg 群の生存例に認められた心筋の変性/線維化は、いずれも限局性でごく軽度な変化であったこと、150/75 mg/kg 群の生存例では同様の変化が認められていないことから、これらの変化はラットおよびマウスで頻繁にみられる自然発生病変[1)]と判断した。

死亡動物では、心筋以外に、腺胃粘膜下織、腎尿細管および子宮筋層などにも変性および壊死がみ

られ、それらの部位および大腿骨では、鉱質沈着あるいは好塩基性物質の沈着が認められた。これらの変化は、フッ化ナトリウムの毒性変化[2)]と類似しており、同様の機序により発現したものと推察される。その他、ハーダー腺の色素沈着過度が死亡動物にみられたが、生存例では認められていない変化であることから、一般状態の悪化に伴った二次的変化の可能性が高いと推察された。

生存例においても、150/75 mg/kg 群では大腿骨の骨端、成長板、骨幹端に好塩基性物質の沈着が認められ、同群の雌雄に切歯の白濁が観察された。大腿骨および切歯にみられた変化は、ヒトのフッ化症[3,4)]に類似したカルシウムやリンの付着によるものと推察されるが、50 mg/kg 以下の群ではこれらの変化は観察されなかった。

尿検査では、150/75 mg/kg 群の非交配雌で尿量が増加し、尿量の増加に伴う変化と考えられる比重、ナトリウムイオン濃度、カリウムイオン濃度および塩素イオン濃度の減少がみられた。腎臓の重量変化や病理組織学検査で異常が認められていないことから、被験物質の刺激性等より飲水量が増加した可能性が考えられる。

血液生化学検査では、50 mg/kg 以上の群の雄に総蛋白濃度の低下、150/75 mg/kg 群の分娩雌に AST と ALP の上昇、さらに 150/75 mg/kg 群の非交配雌に総コレステロールと ALP の上昇がみられ、それらの値は、背景データと比較しても明らかな高値を示した。生存例の肝臓あるいは腎臓の重量および病理組織学検査で関連した変化および所見が認められていないが、大腿骨の病理組織学検査では、好塩基性物質の沈着が 150/75 mg/kg 群に認められており、死亡例で心筋の変性および壊死が認めれらていることから、被験物質投与に関連した変化の可能性は否定できない。

投与終了時の胃の病理組織学検査では、50 mg/kg 以上の群において腺胃の粘膜筋板および粘膜下織に好酸球浸潤と境界縁に樹状細胞様の細胞増加が観察され、同様の変化は死亡動物にも認められていることから被験物質投与による胃粘膜への影響と考えられる。しかし、これらの所見は対照群においても軽度ながら観察されていることから、被験物質の刺激性等より対照群にもみられる変化が増強されたものと推定される。

2. 毒性の回復性

回復観察中の尿検査では 150/75 mg/kg 群の雄において尿量が減少し、血液学検査では同群の雄の MCV については、5 例中 4 例が背景データの範囲を上回った。投与期間中の尿検査および血液学検査では異常が認められていないことから、被験物質の遅発性影響が示唆された。また、回復期間中に、150/75 mg/kg 群の雌雄で体重減少がみられ、切歯の欠落や不正咬合が観察されたことから、被験物質の影響は投与終了後も継続して観察されることが示唆された。しかしながら、回復観察例の病理組織学検査では、腺胃粘膜や大腿骨の組織所見に軽減傾向が認められたことから、これらの毒性は投与終了後に緩やかに回復するものと推察された。なお、回復観察例の病理組織学検査では 150/75 mg/kg 群の雌 1 例に心筋の線維化が認められたが、びまん性で中程度の病変であることから被験物質の影響と考えられ、投与期間中に誘発された心筋の変性または壊死が、その後の時間経過によって線維化に移行したものと推察された。

回復観察中の非交配雌では、紅涙が 150/75 mg/kg 群の 2 例に観察されたが、流涙や流涎などの分泌異常を示唆する変化は認められていないことから、自然発生によるものと判断した。

3. 生殖発生毒性

性周期、交尾率、妊娠率、妊娠期間、出産率、分娩状態、哺育状態、黄体数、着床数および着床率に被験物質投与の影響が認められなかったことから、75 mg/kg までの用量は、親動物の生殖能力に影響を及ぼさないものと考えられる。

出生児の生存性、性比および出生児体重に被験物質投与の影響を示唆する変化は認められず、死亡児あるいは生存児の剖検でも、被験物質投与に起因したと考えられる異常は認められなかったことから、75 mg/kg までの用量は、新生児の発育に影響を及ぼさないと考えられる。

4. 無毒性量

50 mg/kg 以上の群の雌雄において腺胃の粘膜筋板および粘膜下織に好酸球浸潤と境界縁に樹状細胞様の細胞増加が認められたことから、雌雄動物に対する無毒性量(NOAEL)は 15 mg/kg/day と判断された。

150/75 mg/kg 群の親動物ならびに新生児に生殖発生毒性を示唆する変化が認められなかったことから、生殖発生毒性に対する無毒性量は 75 mg/kg/day と判断された。

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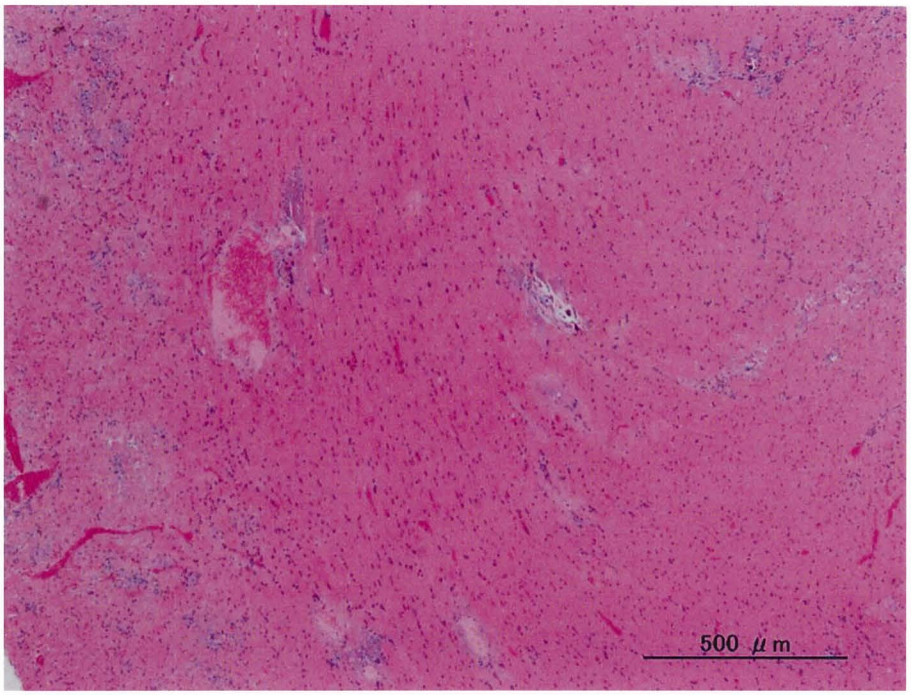

Photo 1 Diffused myocardial degeneration and necrosis with mineralization were observed in dead female of the 150/75 mg/kg group (animal no. F06061).

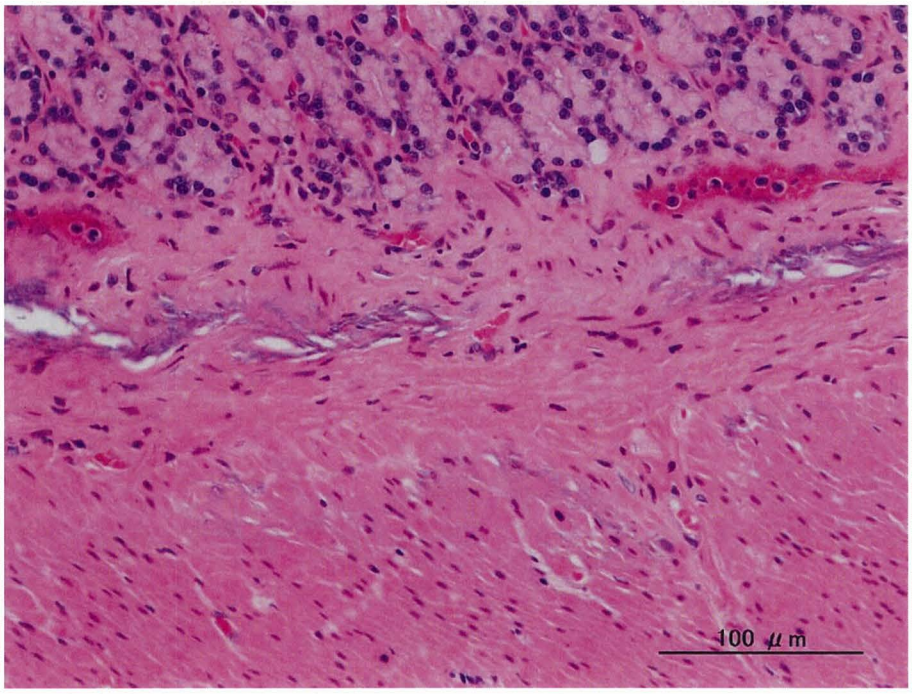

Photo 2 Degeneration and necrosis in the submucosa and smooth muscle with mineralization were observed in dead female of the 150/75 mg/kg group (animal no. F06062).

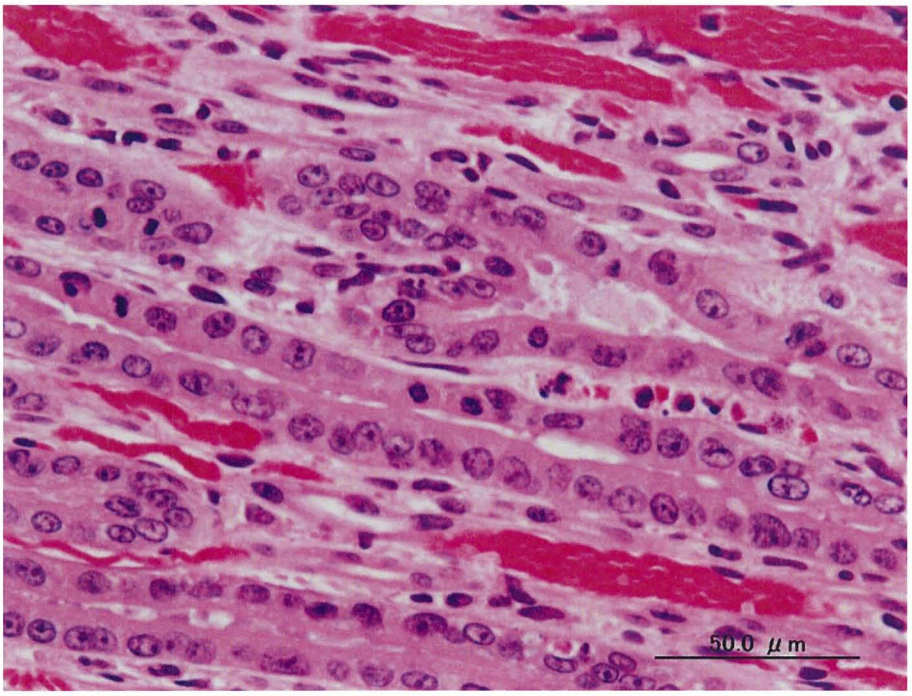

Photo 3 Anisonucleosis, nuclear atypia and increased mitosis in the basophilic collecting ducts were observed in dead femalel of the 150/75 mg/kg group (animal no. F06062).

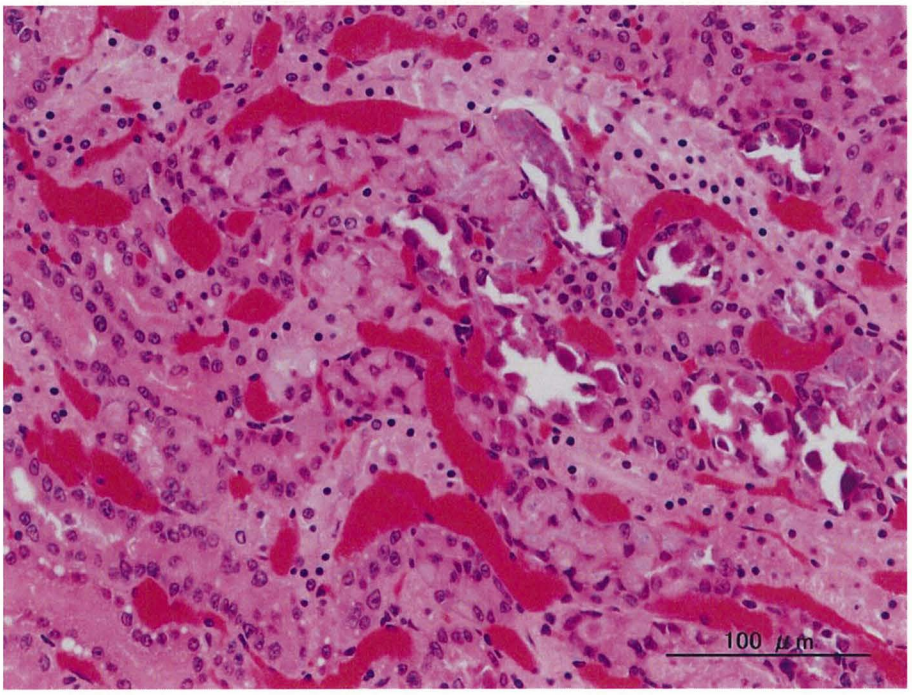

Photo 4 Degeneration and necrosis of the renal tubules with mineralization were observed in dead female of the 150/75 mg/kg group (animal no. F06060).

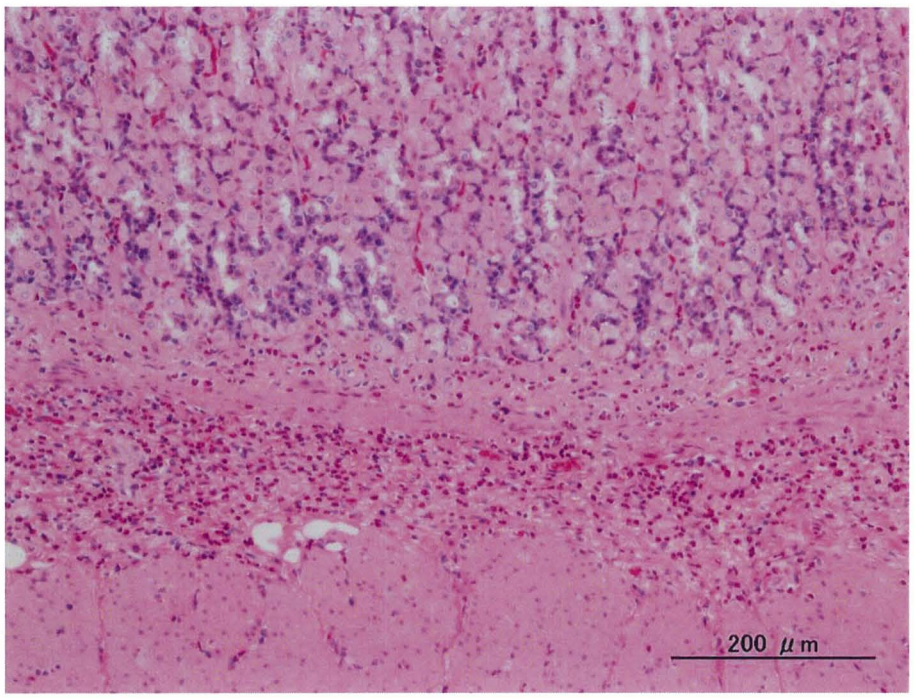

Photo 5 Infiltration of eosinophilic cells in the lamina muscularis mucosa and submucosa of the glandular stomach was observed in a female of the 150/75 mg/kg group (animal no. F06064).

Photo 6 Dendritic-like cells in the mucosa at the limiting ridge were increased in a female of the 150/75 mg/kg group (animal no. F06064).

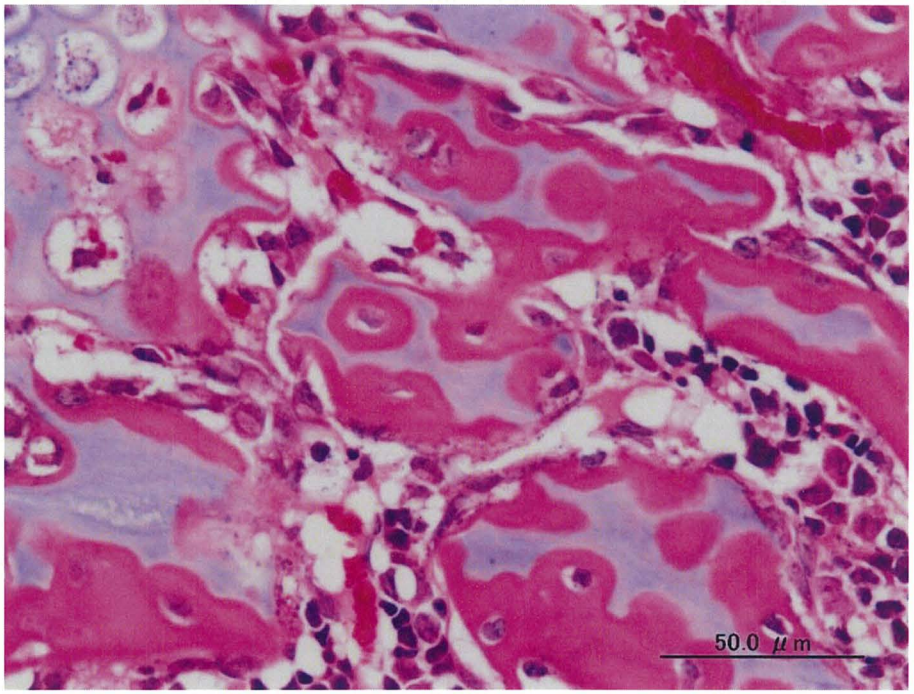

Photo 7 Basophilic deposits in the fumer were observed in a female of the 150/75 mg/kg group (animal no. F06065)

Annex A

SIGMA-ALDRICH®

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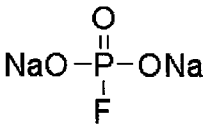
Product Name:
Sodium fluorophosphate - 95%

Product Number:	**344443**
Lot Number:	**MKBJ1508V**
Brand:	ALDRICH
CAS Number:	10163-15-2
MDL Number:	MFCD00014248
Formula:	FNa2O3P
Formula Weight:	143.95 g/mol
Quality Release Date:	30 SEP 2011



Test	Specification	Result
Appearance (Color)	White	White
Appearance (Form)	Powder	Powder
X-Ray Diffraction	Conforms to Structure	Conforms
Titration by HCL	94.0 - 106.0 %	97.3 %

[redacted]

[redacted] Manager
Quality Control
Milwaukee, Wisconsin US

Version Number: 1

Page 1 of 1

Annex B-1

SOP/CHE/001
採用開始 2010年4月23日

試験番号	R－12－008

含 量 試 験 結 果

被験物質：フッ化リン酸二ナトリウム　　調製年月日：2012年11月2日
ロット番号：MKBJ1508V　　測定年月日：2012年11月2日
媒　　体：日局注射用水

試料番号	調製濃度 (A) (mg/mL)	測定濃度 (B) (mg/mL)	平均測定濃度 (C) (mg/mL)	含量 B/A×100 (%)	平均含量 (%)	ばらつき B/C×100 (%)
1	3.00	3.045	3.051	101.5	101.7	99.8
2		3.041		101.4		99.7
3		3.067		102.2		100.5
4	10.0	10.30	10.26	103.0	102.6	100.4
5		10.22		102.2		99.6
6		10.26		102.6		100.0
7	30.0	30.92	31.16	103.1	103.9	99.2
8		31.27		104.2		100.4
9		31.29		104.3		100.4

含量の判断基準(溶液検体)

平均含量が調製濃度の90.0～110.0%、また、各測定値のばらつきがそれぞれ平均値の90.0～110.0%以内とする。

Annex B-2

SOP/CHE/001
採用開始 2010年4月23日

試験番号	R－12－008

含 量 試 験 結 果

被験物質：フッ化リン酸二ナトリウム
ロット番号：MKBJ1508V
媒　　体：日局注射用水

調製年月日：2012年11月30日
測定年月日：2012年11月30日

試料番号	調製濃度 (A) (mg/mL)	測定濃度 (B) (mg/mL)	平均測定濃度 (C) (mg/mL)	含量 B/A×100 (%)	平均含量 (%)	ばらつき B/C×100 (%)
10	15.0	14.98	14.92	99.9	99.5	100.4
11		14.91		99.4		99.9
12		14.88		99.2		99.7

含量の判断基準(溶液検体)

平均含量が調製濃度の90.0～110.0%、また、各測定値のばらつきがそれぞれ平均値の90.0～110.0%以内とする。

Annex C

1. 被験物質原体の安定性の測定方法

① 使用機器

フーリエ変換赤外分光光度計(FTIR-8300)　島津製作所
電子天秤(LA230S)　ザルトリウス

② 測定条件

測定方法　臭化カリウム錠剤法
波数範囲　4000～400 cm^{-1}

③ 測定方法

被験物質1～2 mgをとり、めのう製乳鉢で粉末とし、これに赤外吸収スペクトル用臭化カリウム(島津製作所)0.10～0.20 gを加え、湿気を吸わないように注意し、速やかによくすり混ぜた後、錠剤成型器に入れて加圧製錠する。同様にして対照臭化カリウム錠剤を製する。

2. 投与検体中の被験物質含量測定法

① 試薬

精製水(日本薬局方、以下、水)　小堺製薬
超純水(純水製造装置により製造)

② 使用機器

電子天秤(R200D)　ザルトリウス
イオンクロマトグラフィーシステム(ICS-2000)　日本ダイオネクス

③ 標準溶液の調製

被験物質約10 mgを精密に量り、水に溶解して正確に50 mLとし、標準原液(約200 μg/mL)とする。この標準原液1、1および1.5 mLを正確にとり、水を加えてそれぞれ正確に20、10および10 mLとし、標準溶液(約10、20および30 μg/mL、各濃度n=1)を調製する。

④ 試料溶液の調製

投与検体の1 mLを正確にとり、水で適宜希釈し、試料溶液(約20 μg/mL)を調製する。試料溶液は、投与検体の採取からn=3で調製する。

⑤ 検量線の作成および投与検体中被験物質濃度の算出

試料溶液および標準溶液をイオンクロマトグラフ(IC)により測定する。標準溶液はn=3で測定し、得られたリン酸イオンのピーク面積とSFの調製濃度を基に、検量線を作成する。試料溶液は、各n=1で測定し、得られたリン酸イオンのピーク面積から、先の検量線を用いて、試料溶液中のSF濃度を求める。さらに、希釈係数を乗じて投与検体中のSF濃度を算出し、調製濃度に対する割合(含量、%)および各測定濃度の平均値に対するばらつき(%)を算出する。

⑥ IC 測定条件

検出器	電気伝導度検出器
分析カラム	IonPac AS17 (内径4 mm、長さ250 mm、日本ダイオネクス)
ガードカラム	IonPac AG17 (内径4 mm、長さ50 mm、日本ダイオネクス)
溶離液設定	7 mmol/L水酸化カリウム溶液
流量	1.5 mL/min
サプレッサー	SRS (50 mA)
カラム設定温度	35℃
セル設定温度	35℃
試料設定温度	室温
試料注入量	25 μL
オートインジェクタ洗浄液	超純水
システムの適合性	分析開始前に、標準溶液(約20 μg/mL)を3回測定し、リン酸イオンのピーク保持時間およびピーク面積の相対標準偏差(%)がそれぞれ±3.0%以内および±5.0%以内であることを確認する。

⑦ 数値の取り扱い

1) システム適合性におけるピーク保持時間、ピーク面積は機器の出力値をそのまま使用し、平均値は四捨五入して有効数字3桁まで求める。また、相対標準偏差は四捨五入して小数点以下第1位まで求める。
2) その他はSOP/CHE/001に従い、調製濃度は有効数字4桁目を四捨五入して有効数字3桁で、測定濃度および平均測定濃度は有効数字5桁目を切り捨てて有効数字4桁で表示し、含量、平均含量およびばらつきは小数点以下第2位を四捨五入して少数点以下第1位まで表示する。

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 1-1. General conditions of male rats

Group	Number of males and general conditions	Days of administration																																																	
		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control (vehicle: water for injection)	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Behavior, Decrease in locomotor activity	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	General appearance, Emaciation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Skin, Crust formation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	General appearance, Death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SF 15 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	11	11
	Behavior, Decrease in locomotor activity	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	General appearance, Emaciation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Skin, Crust formation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1
	General appearance, Death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SF 50 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Behavior, Decrease in locomotor activity	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	General appearance, Emaciation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Skin, Crust formation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	General appearance, Death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SF 150/75 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
	Behavior, Decrease in locomotor activity	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	General appearance, Emaciation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Skin, Crust formation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	General appearance, Death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Number of males

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 1-1(continued). General conditions of male rats

Group	Number of males	Days of administration																																		
	and general conditions	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
Control (vehicle: water for injection)	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7
	Skin, Crust formation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SF 15 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Skin, Crust formation	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SF 50 mg/kg	Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
	Skin, Crust formation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SF 150/75 mg/kg	Number of males	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	6
	General appearance, No abnormality	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	6
	Skin, Crust formation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Number of males

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 1-2. General conditions of male rats at the recovery period

Group	Number of males and general conditions	Days of recovery														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Control (vehicle: water for injection)	Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	Mouth, Loss of teeth	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SF 150/75 mg/kg	Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5	4
	Mouth, Loss of teeth	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1
	Number of males															

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 2-1. General conditions of female rats

Group	Number of females and general conditions	Days of administration																																																	
		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control (vehicle: water for injection)	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	9	9	7	7	5	5	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	9	9	7	7	5	5	1	1	1	1	1	1	1	1	1	1	1	1	1	1
SF 15 mg/kg	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	6	6	4	4	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	6	6	4	4	1	1	1	1	1	1	1	1	1	1	1	1	1	1
SF 50 mg/kg	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	9	9	5	5	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	9	9	5	5	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SF 150/75 mg/kg	Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	3	3	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	3	3	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Number of females

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 2-1(continued). General conditions of female rats

Group	Number of females and general conditions	Days of administration																							
		26		27		28		29		30		31		32		33		34		35		36		37	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control (vehicle: water for injection)	Number of females	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	General appearance, No abnormality	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
SF 15 mg/kg	Number of females	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	General appearance, No abnormality	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Group	Number of females and general conditions	Days of administration																									
		38		39		40		41		42		43		44		45		46		47		48		49		50	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control (vehicle: water for injection)	Number of females	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
	General appearance, No abnormality	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
SF 15 mg/kg	Number of females	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	General appearance, No abnormality	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Number of females

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 2-1(continued). General conditions of female rats

Group	Number of females and general conditions	Days of administration				
		51		52		53
		Pre	Post	Pre	Post	Pre
Control (vehicle: water for injection)	Number of females	1	1	1	1	1
	General appearance, No abnormality	1	1	1	1	1
	Number of females					

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 2-2. General conditions of female rats, satellite group

Group	Number of females and general conditions	Days of administration																																																	
		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
Control (vehicle: water for injection)	Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	General appearance, No abnormality	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
	Skin, Reddening of the auricle	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Fur, Hair, Coat, Piloerection	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Eye, Eyeball, Bulbi, Globe, Incomplete eyelid opening	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	General appearance, Emaciation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Eye, Eyeball, Bulbi, Globe, Reddish tear	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Decrease in amount of feces	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	General appearance, Death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Posture, Body position, Prone position	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Nose, Smudge of perinasal area	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Fur, Hair, Coat, Soiled fur	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Skin, Cyanosis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Posture, Body position, Crouching position	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Nervous system, Convulsion	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Body temperature, Hypothermia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SF 150/75 mg/kg	Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	9	9	8	8	8	8	8	8	7
	General appearance, No abnormality	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	8	8	8	8	7	6	6	6	5	7	7
	Skin, Reddening of the auricle	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	1	1	2	2	0	0
	Fur, Hair, Coat, Piloerection	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	1	2	0	0
	Eye, Eyeball, Bulbi, Globe, Incomplete eyelid opening	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	1	1	0	0	0	0
	General appearance, Emaciation	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	1	1	0	0	0	0	1	1	0	0
	Eye, Eyeball, Bulbi, Globe, Reddish tear	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Decrease in amount of feces	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	2	0	0
	General appearance, Death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	1	0
	Posture, Body position, Prone position	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0
	Nose, Smudge of perinasal area	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	1	0	0	0	0
	Fur, Hair, Coat, Soiled fur	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Skin, Cyanosis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
	Posture, Body position, Crouching position	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
	Nervous system, Convulsion	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
	Body temperature, Hypothermia	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0

Number of females

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 2-2(continued). General conditions of female rats, satellite group

Group	Number of females and general conditions	Days of administration																																			
		26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
Control (vehicle: water for injection)	Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5
	General appearance, No abnormality	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5
	Eye, Eyeball, Bulbi, Globe, Reddish tear	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Eye, Eyeball, Bulbi, Globe, Incomplete eyelid opening	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Fur, Hair, Coat, Soiled fur	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Fur, Hair, Coat, Piloerection	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	General appearance, Death	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Posture, Body position, Prone position	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SF 150/75 mg/kg	Number of females	7	7	7	7	7	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	3
	General appearance, No abnormality	7	7	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	5	5	5	5	5	5	3
	Eye, Eyeball, Bulbi, Globe, Reddish tear	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	0
	Eye, Eyeball, Bulbi, Globe, Incomplete eyelid opening	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Fur, Hair, Coat, Soiled fur	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Fur, Hair, Coat, Piloerection	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	General appearance, Death	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Posture, Body position, Prone position	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Number of females																																			

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 2-3. General conditions of female rats at the recovery period

Group	Number of females and general conditions	Days of recovery														
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Control (vehicle: water for injectio	Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	General appearance, No abnormality	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
	Eye, Eyeball, Bulbi, Globe, Reddish tea	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SF 150/75 mg/kg	Number of females	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	General appearance, No abnormality	2	2	2	3	2	2	2	2	3	2	2	3	3	2	3
	Eye, Eyeball, Bulbi, Globe, Reddish tea	1	1	1	0	1	1	1	1	0	1	1	0	0	1	0
	Number of females															

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 3. General conditions in dams during pregnancy

Group	Number of dams and general conditions	Days of pregnancy																																												
		0		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	
Control (vehicle: water for injection)	Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	4
	General appearance, No abnormality	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	4
	Fur, Hair, Coat, Piloerection	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Decrease in amount of feces	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SF 15 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5
	Fur, Hair, Coat, Piloerection	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Decrease in amount of feces	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SF 50 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5
	General appearance, No abnormality	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5
	Fur, Hair, Coat, Piloerection	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Decrease in amount of feces	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
SF 150/75 mg/kg	Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	3
	General appearance, No abnormality	12	12	12	12	12	12	12	12	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	3
	Fur, Hair, Coat, Piloerection	0	0	0	0	0	0	0	0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Excretion, Decrease in amount of feces	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 4. General conditions in dams during lactation

Group	Number of dams and general conditions	Days of lactation										
		0		1		2		3		4		5
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
Control (vehicle: water for injection)	Number of dams	6	6	11	11	11	11	11	11	11	11	11
	General appearance, No abnormality	6	6	11	11	11	11	11	11	11	11	11
	Behavior, Decrease in locomotor activity	0	0	0	0	0	0	0	0	0	0	0
SF 15 mg/kg	Number of dams	9	10	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	9	10	12	12	12	12	12	12	12	12	12
	Behavior, Decrease in locomotor activity	0	0	0	0	0	0	0	0	0	0	0
SF 50 mg/kg	Number of dams	7	7	12	12	12	12	12	12	12	12	12
	General appearance, No abnormality	7	7	12	12	12	12	12	12	12	12	12
	Behavior, Decrease in locomotor activity	0	0	0	0	0	0	0	0	0	0	0
SF 150/75 mg/kg	Number of dams	7	7	11	11	11	11	11	11	11	11	11
	General appearance, No abnormality	7	7	10	10	11	11	11	11	11	11	11
	Behavior, Decrease in locomotor activity	0	0	1	1	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 5. Detailed clinical observations of male rats

Findings	Group	Initial number of animals	Pre-treatment	Days of treatment											Days of recovery			
				8	15		24		30		36		42		7		14	
[Behavior while removing from cage]	Control (vehicle: water for injection)	12	0 [a]	0	1		0		0		1		0		0	(5)	0	(5)
	SF 15 mg/kg	12	0	0	0		0		0		0		0					
Hard	SF 50 mg/kg	12	0	0	1		0		0		0		0					
	SF 150/75 mg/kg	12	0	0	0	(11)	0	(11)	0	(11)	0	(11)	0	(11)	0	(5)	0	(5)
[Lacrimation]	Control (vehicle: water for injection)	12	0 [a]	0	0		0		0		0		0		0	(5)	0	(5)
Slight	SF 15 mg/kg	12	0	0	0		0		0		0		0					
	SF 50 mg/kg	12	0	0	0		0		0		0		0					
	SF 150/75 mg/kg	12	0	0	0	(11)	0	(11)	0	(11)	0	(11)	0	(11)	0	(5)	0	(5)
[Vocalization]	Control (vehicle: water for injection)	12	0 [a]	0	0		0		0		0		0		0	(5)	0	(5)
Heard	SF 15 mg/kg	12	0	0	0		0		0		0		0					
	SF 50 mg/kg	12	0	0	4		0		0		0		0					
	SF 150/75 mg/kg	12	0	0	0	(11)	0	(11)	0	(11)	0	(11)	0	(11)	0	(5)	0	(5)
[Touch response]	Control (vehicle: water for injection)	12	0 [a]	0	0		0		0		1		0		0	(5)	0	(5)
Sensitive	SF 15 mg/kg	12	0	0	0		0		0		0		0					
	SF 50 mg/kg	12	0	0	1		0		0		0		0					
	SF 150/75 mg/kg	12	0	0	0	(11)	0	(11)	0	(11)	1	(11)	0	(11)	0	(5)	0	(5)
[Urination]	Control (vehicle: water for injection)	12	3 [b]	1	4		1		1		2		1		2	(5)	1	(5)
(frequency/30sec)	SF 15 mg/kg	12	1	3	4		1		1		2		2					
	SF 50 mg/kg	12	2	0	3		0		0		2		1					
	SF 150/75 mg/kg	12	7	0	3	(11)	0	(11)	1	(11)	4	(11)	2	(11)	1	(5)	1	(5)
[Defecation]	Control (vehicle: water for injection)	12	1 [b]	1	0		0		2		0		0		0	(5)	0	(5)
(frequency/30sec)	SF 15 mg/kg	12	0	2	4		0		0		0		0					
	SF 50 mg/kg	12	1	0	1		0		0		1		0					
	SF 150/75 mg/kg	12	4	0	0	(11)	0	(11)	0	(11)	0	(11)	0	(11)	0	(5)	0	(5)

[a] Values represent number of animals with the findings.
[b] Values represent total score of each group.
Figures in parenthese indicate number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 6-1. Detailed clinical observations of female rats

Findings	Group	Initial number of animals	Pre-treatment	Days of treatment 8	15	24	30	36	The lactation period
[Behavior while removing from cage] Hard	Control (vehicle: water for injection)	12	0 [a]	0	0	0	0	0	0 (11)
	SF 15 mg/kg	12	0	0	0	0	0	0	0
	SF 50 mg/kg	12	0	0	0	0	0	0	0
	SF 150/75 mg/kg	12	0	0	0	0 (11)	0 (11)	0 (11)	0 (11)
[Lacrimation] Slight	Control (vehicle: water for injection)	12	0 [a]	0	0	0	0	0	0 (11)
	SF 15 mg/kg	12	0	0	0	0	0	0	0
	SF 50 mg/kg	12	0	0	0	0	0	0	0
	SF 150/75 mg/kg	12	0	0	0	0 (11)	0 (11)	0 (11)	0 (11)
[Vocalization] Heard	Control (vehicle: water for injection)	12	0 [a]	0	0	0	0	0	0 (11)
	SF 15 mg/kg	12	0	0	0	0	0	0	0
	SF 50 mg/kg	12	0	0	0	0	0	0	0
	SF 150/75 mg/kg	12	0	0	0	0 (11)	0 (11)	0 (11)	0 (11)
[Touch response] Sensitive	Control (vehicle: water for injection)	12	0 [a]	0	0	0	0	0	0 (11)
	SF 15 mg/kg	12	0	0	0	0	0	0	0
	SF 50 mg/kg	12	0	0	0	0	0	0	0
	SF 150/75 mg/kg	12	0	0	0	0 (11)	0 (11)	0 (11)	0 (11)
[Urination] (frequency/30sec)	Control (vehicle: water for injection)	12	2 [b]	1	1	2	1	0	2 (11)
	SF 15 mg/kg	12	0	2	1	1	2	1	0
	SF 50 mg/kg	12	0	0	0	0	0	1	2
	SF 150/75 mg/kg	12	1	0	0	2 (11)	1 (11)	1 (11)	2 (11)
[Defecation] (frequency/30sec)	Control (vehicle: water for injection)	12	1 [b]	0	0	1	0	1	1 (11)
	SF 15 mg/kg	12	0	0	0	0	0	0	0
	SF 50 mg/kg	12	0	0	0	0	0	0	0
	SF 150/75 mg/kg	12	0	0	0	1 (11)	1 (11)	0 (11)	0 (11)

[a] Values represent number of animals with the findings.
[b] Values represent total score of each group.
Figures in parenthese indicate number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 6-2. Detailed clinical observations of female rats, satellite group

Findings	Group	Initial number of animals	Pre-treatment	Days of treatment										Days of recovery			
				8	15	24		30		36		42		7		14	
[Behavior while removing from cage] Hard	Control (vehicle: water for injection)	10	0 [a]	0	0	0		0		0		0		0	(5)	0	(5)
	SF 150/75 mg/kg	10	0	0	0	0	(7)	0	(6)	0	(6)	0	(6)	0	(3)	0	(3)
[Lacrimation] Slight	Control (vehicle: water for injection)	10	0 [a]	0	0	0		0		0		0		0	(5)	0	(5)
	SF 150/75 mg/kg	10	0	0	0	0	(7)	0	(6)	0	(6)	0	(6)	0	(3)	1	(3)
[Vocalization] Heard	Control (vehicle: water for injection)	10	0 [a]	0	0	0		0		0		0		0	(5)	0	(5)
	SF 150/75 mg/kg	10	0	0	0	0	(7)	0	(6)	0	(6)	0	(6)	0	(3)	0	(3)
[Touch response] Sensitive	Control (vehicle: water for injection)	10	0 [a]	0	0	0		0		0		0		0	(5)	0	(5)
	SF 150/75 mg/kg	10	0	0	0	0	(7)	0	(6)	0	(6)	0	(6)	0	(3)	0	(3)
[Urination] (frequency/30sec)	Control (vehicle: water for injection)	10	0 [b]	0	0	0		0		0		0		0	(5)	0	(5)
	SF 150/75 mg/kg	10	0	0	0	0	(7)	0	(6)	1	(6)	1	(6)	0	(3)	0	(3)
[Defecation] (frequency/30sec)	Control (vehicle: water for injection)	10	0 [b]	0	0	0		0		0		0		0	(5)	0	(5)
	SF 150/75 mg/kg	10	0	0	0	0	(7)	0	(6)	0	(6)	0	(6)	0	(3)	0	(3)

[a] Values represent number of animals with the findings.
[b] Values represent total score of each group.
Figures in parenthese indicate number of animals.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 7-1. Body weights of male rats

Group	Control (vehicle: water for injection)	SF 15 mg/kg	SF 50 mg/kg	SF 150/75 mg/kg	
Number of males	12	12	12	12	
Days of administration					
1	374.9 ± 15.2	371.4 ± 18.0	370.6 ± 14.5	374.4 ± 13.4	
4	384.1 ± 19.3	381.2 ± 18.6	382.2 ± 16.9	381.3 ± 17.3	
7	400.5 ± 22.3	395.2 ± 19.2	394.8 ± 18.0	392.4 ± 20.3	
14	424.8 ± 24.9	417.6 ± 26.3	416.1 ± 20.3	410.8 ± 33.8	
21	442.2 ± 29.0	437.2 ± 24.8	437.2 ± 22.9	439.4 ± 24.1	(11)
28	456.8 ± 32.2	454.3 ± 27.7	454.5 ± 27.0	456.8 ± 27.8	(11)
35	473.2 ± 34.7	471.7 ± 31.2	474.6 ± 30.7	480.8 ± 26.9	(11)
42	483.1 ± 34.3	479.7 ± 35.0	486.7 ± 31.4	487.0 ± 34.7	(11)

Each value shows mean (g) ± S.D.
Significantly different from the control group (*: P<0.05, **: P<0.01).
Figures in parentheses indicate number of males.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 7-2. Body weights of male rats at the recovery period

Group	Control (vehicle: water for injection)	SF 150/75 mg/kg
Number of males	5	5
Days of recovery		
1	482.7 ± 32.4	492.2 ± 47.6
7	498.9 ± 30.8	507.2 ± 47.5
14	512.2 ± 30.6	489.4 ± 37.4

Each value shows mean (g) ± S.D.
Significantly different from the control group (*: P<0.05, **: P<0.01).
Figures in parentheses indicate number of males.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 8-1. Body weights of female rats

Group		Control (vehicle: water for injection)	SF 15 mg/kg	SF 50 mg/kg	SF 150/75 mg/kg
Number of females		11	12	12	12
Days of administration					
	1	237.3 ± 10.5	235.8 ± 11.9	230.7 ± 11.5	233.3 ± 14.7
	4	240.9 ± 11.4	240.3 ± 12.3	237.1 ± 11.7	242.2 ± 14.0
	7	246.1 ± 11.8	245.0 ± 11.7	243.2 ± 16.6	244.9 ± 14.0
	14	256.6 ± 17.2	255.7 ± 16.5	251.4 ± 16.1	253.6 ± 15.4

Each value shows mean (g) ± S.D.
Significantly different from the control group (*: P<0.05, **: P<0.01).
Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 8-2. Body weights of female rats, satellite group

Group	Control (vehicle: water for injection)	SF 150/75 mg/kg	
Number of females	10	10	
Days of administration			
1	236.5 ± 10.4	233.9 ± 12.0	
4	242.4 ± 10.5	240.0 ± 9.9	
7	250.4 ± 11.9	244.8 ± 10.8	
14	258.9 ± 13.1	255.2 ± 11.2	
21	264.7 ± 15.0	256.0 ± 26.8	(9)
28	271.0 ± 16.7	265.8 ± 16.0	(6)
35	277.7 ± 18.3	273.7 ± 16.9	(6)
42	279.9 ± 17.8	273.8 ± 14.5	(6)

Each value shows mean (g) ± S.D.
Significantly different from the control group (*: P<0.05, **: P<0.01).
Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 8-3. Body weights of female rats at the recovery period

Group	Control (vehicle: water for injection)	SF 150/75 mg/kg
Number of females	5	3
Days of recovery		
1	284.8 ± 21.2	288.1 ± 15.5
7	295.3 ± 26.1	292.0 ± 16.7
14	293.7 ± 25.7	277.1 ± 7.7

Each value shows mean (g) ± S.D.
Significantly different from the control group (*: P<0.05, **: P<0.01).
Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 9. Body weights of dams during pregnancy

Group	Control (vehicle: water for injection)	SF 15 mg/kg	SF 50 mg/kg	SF 150/75 mg/kg
Number of dams	11	12	12	11
Days of pregnancy				
0	263.4 ± 18.2	265.5 ± 19.8	257.4 ± 16.7	260.9 ± 18.8
7	296.8 ± 15.5	298.5 ± 22.5	295.8 ± 20.5	294.3 ± 14.7
14	333.4 ± 20.5	332.6 ± 23.6	333.9 ± 26.4	332.2 ± 15.5
20	417.5 ± 24.8	414.3 ± 23.2	417.4 ± 30.6	413.6 ± 18.9

Each value shows mean ± S.D. (g).

Figures in parentheses indicate number of dams.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 10. Body weights of dams during lactation

Group		Control (vehicle: water for injection)	SF 15 mg/kg	SF 50 mg/kg	SF 150/75 mg/kg
Number of dams		11	12	12	11
Days of lactation					
	0	311.3 ± 20.0	312.0 ± 28.0	324.0 ± 26.5	309.7 ± 15.2
	4	325.8 ± 20.9	327.1 ± 19.1	327.6 ± 21.0	317.0 ± 18.4

Each value shows mean ± S.D. (g).
Figures in parentheses indicate number of dams.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 11-1. Food consumption of male rats

Group	Control (vehicle: water for injection)	SF 15 mg/kg	SF 50 mg/kg	SF 150/75 mg/kg	
Number of males	12	12	12	12	
Days of administration					
1	30.8 ± 2.8	30.0 ± 2.2	29.8 ± 4.5	27.6 ± 2.6	
7	27.0 ± 2.9	25.7 ± 3.0	27.4 ± 2.4	26.1 ± 2.5	
14	26.5 ± 2.7	24.6 ± 2.7	26.7 ± 3.0	24.0 ± 7.2	
29	26.4 ± 2.1	27.6 ± 2.9	27.0 ± 2.5	29.0 ± 2.4	(11)
35	29.9 ± 2.9	30.4 ± 2.8	31.2 ± 2.9	30.3 ± 2.3	(11)
41	29.0 ± 2.2	28.7 ± 3.3	28.9 ± 2.9	27.7 ± 3.5	(11)

Each value shows mean (g) ± S.D.
Significantly different from the control group (*: P<0.05, **: P<0.01).
Figures in parentheses indicate number of males.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 11-2. Food consumption of male rats at the recovery period

Group	Control (vehicle: water for injection)	SF 150/75 mg/kg
Number of males	5	5
Days of recovery		
6	30.4 ± 2.3	28.4 ± 5.0
12	30.4 ± 2.3	28.3 ± 1.8

Each value shows mean (g) ± S.D.
Significantly different from the control group (*: P<0.05, **: P<0.01).
Figures in parentheses indicate number of males.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 12-1. Food consumption of female rats

Group	Control (vehicle: water for injection)	SF 15 mg/kg	SF 50 mg/kg	SF 150/75 mg/kg
Number of females	12	12	12	12
Days of administration				
1	20.2 ± 2.3	20.0 ± 3.0	19.0 ± 3.4	18.6 ± 3.6
7	19.6 ± 2.7	19.4 ± 3.6	19.4 ± 2.7	19.1 ± 2.1
14	18.9 ± 3.1	19.5 ± 3.0	20.3 ± 3.5	20.4 ± 2.1

Each value shows mean (g) ± S.D.
Significantly different from the control group (*: P<0.05, **: P<0.01).
Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 12-2. Food consumption of female rats, satellite group

Group	Control (vehicle: water for injection)				SF 150/75 mg/kg			
Number of females		10				10		
Days of administration								
	1	20.6	±	2.1	18.3	±	2.9	
	7	19.3	±	2.6	19.1	±	2.3	
	14	19.7	±	2.9	19.1	±	3.1	
	21	21.0	±	2.6	19.6	±	3.8	(8)
	29	19.8	±	5.8	19.2	±	4.5	(6)
	35	21.0	±	2.2	19.7	±	2.3	(6)
	41	18.4	±	3.7	18.4	±	1.5	(6)

Each value shows mean (g) ± S.D.
Significantly different from the control group (*: P<0.05, **: P<0.01).
Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 12-3. Food consumption of female rats at the recovery period

Group	Control (vehicle: water for injection)	SF 150/75 mg/kg
Number of females	5	3
Days of recovery		
6	23.1 ± 3.1	21.2 ± 3.3
12	20.3 ± 4.6	18.5 ± 1.6

Each value shows mean (g) ± S.D.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Figures in parentheses indicate number of females.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 13. Food consumption in dams during pregnancy

Group	Control (vehicle: water for injection)	SF 15 mg/kg	SF 50 mg/kg	SF 150/75 mg/kg
Number of dams	11	12	12	11
Days of pregnancy				
0	21.2 ± 1.8	22.4 ± 2.6	20.0 ± 2.4	21.6 ± 2.3
7	25.6 ± 2.2	26.2 ± 3.9	27.5 ± 3.7	26.2 ± 3.0
14	27.2 ± 2.1	26.0 ± 4.3	29.2 ± 3.1	28.1 ± 2.9
20	23.9 ± 2.5	24.8 ± 5.1	26.1 ± 3.2	23.4 ± 4.2

Each value shows mean ± S.D. (g).
Figures in parentheses indicate number of dams.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 14. Food consumption in dams during lactation

Group	Control (vehicle: water for injection)	SF 15 mg/kg	SF 50 mg/kg	SF 150/75 mg/kg
Number of dams	11	12	12	11
Days of lactation				
3	43.2 ± 4.4	43.3 ± 6.4	43.2 ± 4.0	41.1 ± 9.5

Each value shows mean ± S.D. (g).
Figures in parentheses indicate number of dams.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 15. Functional findings of male rats at the last week of the dosing period

Group	Cotrol (vehicle: water for injection)	SF (15 mg/kg)	SF (50 mg/kg)	SF (150/75 mg/kg)
Male				
Number of animals	5	5	5	5
Righting reflex	100	100	100	100
Visual placing	100	100	100	100
Pupillary reflex	100	100	100	100
Startle reaction	100	100	100	100
Preyer's reaction	100	100	100	100
Withdrawal reflex	100	100	100	100
Eyelid reflex	100	100	100	100

Values represent % of animals showing normal responses.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 16. Functional findings of female rats at the last week of the dosing period

Group	Cotrol (vehicle: water for injection)	SF (15 mg/kg)	SF (50 mg/kg)	SF (150/75 mg/kg)
Female, dam				
Number of animals	5	5	5	5
Righting reflex	100	100	100	100
Visual placing	100	100	100	100
Pupillary reflex	100	100	100	100
Startle reaction	100	100	100	100
Preyer's reaction	100	100	100	100
Withdrawal reflex	100	100	100	100
Eyelid reflex	100	100	100	100
Female, satelite group				
Number of animals	5			5
Righting reflex	100			100
Visual placing	100			100
Pupillary reflex	100			100
Startle reaction	100			100
Preyer's reaction	100			100
Withdrawal reflex	100			100
Eyelid reflex	100			100

Values represent % of animals showing normal responses.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 17. Assessment of grip strength of male rats at the last week of the dosing period

Group	Control (vehicle: water for injection)	SF (15 mg/kg)	SF (50 mg/kg)	SF(150/75 mg/kg)
Number of males	5	5	5	5
Forelimb	1.140 ± 0.079	1.140 ± 0.085	1.126 ± 0.040	1.132 ± 0.066
Hindlimb	0.871 ± 0.093	0.842 ± 0.081	0.810 ± 0.076	0.899 ± 0.032

Each value shows mean (kg) ±S.D.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 18. Assessment of grip strength of female rats at the last week of the dosing period

Group	Control (vehicle: water for injection)	SF (15 mg/kg)	SF (50 mg/kg)	SF (150/75 mg/kg)
Number of females	5	5	5	5
Forelimb	1.118 ± 0.127	1.049 ± 0.050	1.117 ± 0.087	1.142 ± 0.103
Hindlimb	0.749 ± 0.048	0.736 ± 0.118	0.699 ± 0.060	0.655 ± 0.126

Each value shows mean (kg) ±S.D.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 19. Assessment of grip strength of female rats at the last week of the dosing period, satellite group

Group	Control (vehicle: water for injection)	SF (150/75 mg/kg)
Number of females	5	5
Forelimb	1.117 ± 0.042	1.158 ± 0.082
Hindlimb	0.770 ± 0.093	0.782 ± 0.090

Each value shows mean (kg) ±S.D.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 20. Motor activity of male rats at the last week of the dosing period

Group	Control (vehicle: water for injection)	SF (15 mg/kg)	SF (50 mg/kg)	SF (150/75 mg/kg)
Number of males	5	5	5	5
Ambulation (counts)				
5min	1177 ± 137	1179 ± 180	1080 ± 167	1219 ± 347
10min	1155 ± 160	1119 ± 174	1030 ± 162	1048 ± 394
15min	1040 ± 173	1055 ± 225	826 ± 176	827 ± 405
20min	751 ± 286	828 ± 458	741 ± 262	585 ± 332
Total	4123 ± 664	4180 ± 947	3677 ± 598	3678 ± 1385
Rearing (counts)				
5min	38 ± 3	38 ± 11	38 ± 7	33 ± 8
10min	29 ± 7	29 ± 9	30 ± 9	19 ± 5
15min	29 ± 10	27 ± 9	21 ± 9	14 ± 6
20min	16 ± 10	23 ± 18	21 ± 7	8 ± 6
Total	112 ± 21	118 ± 42	109 ± 19	74 ± 14

Each value shows mean±S.D.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 21. Motor activity of female rats at the last week of the dosing period

Group	Ccontrol (vehicle: water for injection)	SF (15 mg/kg)	SF (50 mg/kg)	SF (150/75 mg/kg)
Number of females	5	5	5	5
Ambulation (counts)				
5min	913 ± 141	1103 ± 55	1108 ± 71	1249 ± 249 *
10min	516 ± 242	808 ± 120	928 ± 117	887 ± 390
15min	406 ± 148	477 ± 197	616 ± 314	721 ± 267
20min	331 ± 185	405 ± 81	634 ± 178	559 ± 360
Total	2166 ± 542	2794 ± 227	3286 ± 530 *	3415 ± 1038 *
Rearing (counts)				
5min	25 ± 9	29 ± 3	30 ± 4	30 ± 6
10min	14 ± 12	12 ± 3	18 ± 5	14 ± 10
15min	7 ± 8	5 ± 5	7 ± 6	10 ± 5
20min	3 ± 5	6 ± 4	8 ± 5	5 ± 7
Total	49 ± 34	51 ± 5	62 ± 5	58 ± 20

Each value shows mean±S.D.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 22. Motor activity of female rats at the last week of the dosing period, satellite group

Group	Control (vehicle: water for injection)	SF (150/75 mg/kg)
Number of females	5	5
Ambulation (counts)		
5min	1133 ± 115	1160 ± 95
10min	1014 ± 277	1096 ± 131
15min	868 ± 248	1032 ± 163
20min	913 ± 226	899 ± 451
Total	3928 ± 779	4187 ± 734
Rearing (counts)		
5min	34 ± 13	36 ± 4
10min	32 ± 20	32 ± 5
15min	25 ± 20	31 ± 6
20min	29 ± 22	27 ± 18
Total	121 ± 66	127 ± 20

Each value shows mean±S.D.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 23-1. Urinalysis in male rats

Group	Number of males	Quality[a)]																
		Color	Turbidity	pH				Protein			Glucose	Ketone			Bilirubin	Occult blood	Urobilinogen	
		Light yellow	-	6.0	6.5	7.0	7.5	±	+	2+	-	-	±	+	-	-	±	+
Control (vehicle: water for injection)	5	5	5	0	0	3	2	1	3	1	5	2	3	0	5	5	5	0
SF (15 mg/kg)	5	5	5	1	1	3	0	1	4	0	5	1	3	1	5	5	4	1
SF (50 mg/kg)	5	5	5	3	2	0	0	0	5	0	5	1	3	1	5	5	4	1
SF (150/75 mg/kg)	5	5	5	0	5	0	0	0	5	0	5	1	4	0	5	5	3	2

Group	Number of males	Urinary sediments[a)]							Urine volume[b)]	Specific gravity[b)]	Electrolyte, density[b)] (mEq/L)			Electrolyte, gross volume[b)] (mEq/24 hr)		
		Red blood cells	White blood cells	Casts	Crystals		Epithelial cells									
		-	-	-	-	±	−	±	(mL/24hr)		Na	K	Cl	Na	K	Cl
Control (vehicle: water for injection)	5	5	5	5	1	4	5	0	18.3 ±7.1	1.054 ±0.016	89.9 ±33.0	172.5 ±37.3	111.1 ±41.2	1.49 ±0.32	2.96 ±0.39	1.83 ±0.24
SF (15 mg/kg)	5	5	5	5	1	4	5	0	15.3 ±4.8	1.060 ±0.011	116.3 ±19.8	169.6 ±28.0	128.0 ±24.5	1.71 ±0.28	2.52 ±0.57	1.89 ±0.38
SF (50 mg/kg)	5	5	5	5	4	1	5	0	18.5 ±4.7	1.056 ±0.012	89.4 ±22.5	156.1 ±29.6	107.6 ±20.1	1.60 ±0.38	2.78 ±0.33	1.93 ±0.29
SF (150/75 mg/kg)	5	5	5	5	1	4	4	1	18.8 ±4.2	1.051 ±0.012	114.6 ±44.0	163.7 ±35.8	93.5 ±45.0	2.08 ±0.66	3.01 ±0.59	1.71 ±0.77

Significantly different from the control group (*: P<0.05, **: P<0.01).
Turbidity, -: negative
Protein, ±: 10≦and<30 mg/dL; +: 30≦and<100 mg/dL; 2+: 100≦and<300 mg/dL
Glucose, -: negative
Ketone, -: negative; ±: 5≦and<10 mg/dL; +: 10≦and<40 mg/dL; 2+: 40≦and<80 mg/dL
Bilirubin, -: negative
Occult blood, -: negative
Urobilinogen, ±: normal; +: 2.0≦and<4.0 mg/dL; 2+: 4.0≦and<8.0 mg/dL
Red blood cells, White blood cells and Casts, -: not observed
Crystals and Epithelial cells, -: not observed; ±: a few
a), values represent as number of animals
b), values represent as mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 23-2. Urinalysis in male rats of the recovery period

Group	Number of males	Quality[a)]																		
		Color	Turbidity	pH					Protein		Glucose	Ketone		Bilirubin	Occult blood		Urobilinogen		
		Light yellow	-	6.5	7.0	7.5	8.0	8.5	+	2+	-	±	+	-	-	±	±	+	2+
Ccontrol (vehicle: water for injection)	5	5	5	1	1	2	0	1	4	1	5	3	2	5	4	1	3	2	0
SF (150/75 mg/kg)	5	5	5	1	3	1	0	0	3	2	5	2	3	5	5	0	0	4	1

Group	Number of males	Urinary sediments[a)]							Urine volume[b)]	Specific gravity[b)]	Electrolyte, density[b)] (mEq/L)			Electrolyte, gross volume[b)] (mEq/24 hr)		
		Red blood cells	White blood cells	Casts	Crystals		Epithelial cells									
		-	-	-	±	+	-	±	(mL/24hr)		Na	K	Cl	Na	K	Cl
Ccontrol (vehicle: water for injection)	5	5	5	5	4	1	5	0	15.7 ±1.9	1.065 ±0.010	119.7 ±25.9	232.7 ±28.6	140.8 ±32.4	1.85 ±0.27	3.61 ±0.23	2.17 ±0.31
SF (150/75 mg/kg)	5	5	5	5	4	1	5	0	10.2** ±2.7	1.066 ±0.010	96.7 ±19.3	203.6 ±20.5	80.6 * ±30.4	0.98** ±0.30	2.08** ±0.60	0.86** ±0.51

Significantly different from the control group (*: P<0.05, **: P<0.01).
Turbidity, -: negative
Protein, ±: 10≦and<30 mg/dL; +: 30≦and<100 mg/dL; 2+: 100≦and<300 mg/dL
Glucose, -: negative
Ketone, -: negative; ±: 5≦and<10 mg/dL; +: 10≦and<40 mg/dL; 2+: 40≦and<80 mg/dL
Bilirubin, -: negative
Occult blood, -: negative
Urobilinogen, ±: normal; +: 2.0≦and<4.0 mg/dL; 2+: 4.0≦and<8.0 mg/dL
Red blood cells, White blood cells and Casts, -: not observed
Crystals and Epithelial cells, -: not observed; ±: a few
a), values represent as number of animals
b), values represent as mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 24-1. Urinalysis in female rats, satellite group

Group	Number of females	Quality[a)]																			
		Color	Turbidity		pH				Protein				Glucose	Ketone			Bilirubin	Occult blood	Urobilinogen	
		Light yellow	-	+	5.5	6.0	6.5	7.0	-	±	+	2+	-	-	±	+	-	-	±	+
Control (vehicle: water for injection)	5	5	5	0	0	1	1	3	3	1	1	0	5	4	0	1	5	5	4	1
SF (150/75 mg/kg)	5	5	4	1	1	3	1	0	3	1	0	1	5	4	1	0	5	5	5	0

Group	Number of females	Urinary sediments[a)]							Urine volume[b)]	Specific gravity[b)]	Electrolyte, density[b)] (mEq/L)			Electrolyte, gross volume[b)] (mEq/24 hr)		
		Red blood cells	White blood cells	Casts	Crystals		Epithelial cells									
		-	-	-	-	±	-	±	(mL/24hr)		Na	K	Cl	Na	K	Cl
Control (vehicle: water for injection)	5	5	5	5	1	4	5	0	9.6 ±3.3	1.060 ±0.007	100.7 ±23.6	176.1 ±13.9	109.5 ±20.8	0.94 ±0.28	1.70 ±0.54	1.05 ±0.37
SF (150/75 mg/kg)	5	5	5	5	5	0	3	2	14.5 * ±2.7	1.041 * ±0.012	59.5** ±11.6	123.8 * ±34.8	54.1 * ±37.6	0.86 ±0.24	1.79 ±0.57	0.78 ±0.57

Significantly different from the control group (*: P<0.05, **: P<0.01).
Turbidity, -: negative +: slight
Protein, -: negative; ±: 10≦and<30 mg/dL; +: 30≦and<100 mg/dL
Glucose, -: negative
Ketone, -: negative; ±: 5≦and<10 mg/dL; +: 10≦and<40 mg/dL
Bilirubin, -: negative
Occult blood, -: negative
Urobilinogen, ±: normal; +: 2.0≦and<4.0 mg/dL
Red blood cells, White blood cells and Casts, -: not observed
Crystals and Epithelial cells, -: not observed; ±: a few
a), values represent as number of animals
b), values represent as mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 24-2. Urinalysis in female rats of the recovery period

Group	Number of females	Quality[a)]																	
		Color	Turbidity	pH			Protein			Glucose	Ketone			Bilirubin	Occult blood	Urobilinogen		
		Light yellow	-	6.5	7.0	7.5	-	±	+	-	-	±	+	-	-	±	+	2+
Control (vehicle: water for injection)	5	5	5	3	1	1	2	0	3	5	2	1	2	5	5	3	1	1
SF (150/75 mg/kg)	3	3	3	2	1	0	1	2	0	3	3	0	0	3	3	1	2	0

Group	Number of females	Urinary sediments[a)]						Urine volume[b)]	Specific gravity[b)]	Electrolyte, density[b)] (mEq/L)			Electrolyte, gross volume[b)] (mEq/24 hr)		
		Red blood cells	White blood cells	Casts	Crystals		Epithelial cells								
		-	-	-	-	±	-	(mL/24hr)		Na	K	Cl	Na	K	Cl
Control (vehicle: water for injection)	5	5	5	5	3	2	5	11.2 ±5.6	1.056 ±0.018	102.7 ±35.1	193.0 ±50.2	117.8 ±44.5	1.07 ±0.38	2.08 ±0.83	1.25 ±0.50
SF (150/75 mg/kg)	3	3	3	3	1	2	3	13.3 ±6.4	1.050 ±0.015	90.2 ±20.1	172.9 ±43.8	89.6 ±27.5	1.16 ±0.53	2.23 ±1.11	1.22 ±0.65

Significantly different from the control group (*: P<0.05, **: P<0.01).
Turbidity, -: negative
Protein, -: negative; ±: 10≦and<30 mg/dL; +: 30≦and<100 mg/dL; 2+: 100≦and<300 mg/dL
Glucose, -: negative
Ketone, -: negative; ±: 5≦and<10 mg/dL; +: 10≦and<40 mg/dL
Bilirubin, -: negative
Occult blood, -: negative
Urobilinogen, ±: normal; +: 2.0≦and<4.0 mg/dL
Red blood cells, White blood cells and Casts, -: not observed
Crystals and Epithelial cells, -: not observed; ±: a few
a), values represent as number of animals
b), values represent as mean ± S.D.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 25-1. Hematological findings of male rats at the end of the dosing period

Group	Control (vehicle: water for injection)	SF (15 mg/kg)	SF (50 mg/kg)	SF (150/75 mg/kg)
Number of males	5	5	5	5
RBC ($\times 10^4/\mu L$)	833 ± 46	840 ± 59	814 ± 31	816 ± 47
Hemoglobin (g/dL)	15.3 ± 0.6	15.2 ± 1.0	15.3 ± 0.3	15.0 ± 0.6
Hematocrit (%)	43.2 ± 1.8	43.1 ± 2.1	43.9 ± 2.0	43.3 ± 1.6
MCV (fL)	51.8 ± 1.4	51.4 ± 1.7	54.0 ± 4.2	53.1 ± 1.8
MCH (pg)	18.4 ± 0.5	18.1 ± 0.2	18.8 ± 0.9	18.5 ± 0.5
MCHC (g/dL)	35.5 ± 0.4	35.2 ± 1.0	34.9 ± 1.0	34.8 ± 0.6
Platelet ($\times 10^4/\mu L$)	114.0 ± 11.1	107.5 ± 11.8	105.8 ± 11.0	121.5 ± 11.2
PT (sec)	20.1 ± 6.3	20.4 ± 3.0	21.3 ± 2.7	18.9 ± 4.4
APTT (sec)	26.8 ± 3.1	27.3 ± 1.1	28.1 ± 2.2	25.6 ± 3.6
WBC ($\times 10^2/\mu L$)	75.2 ± 18.9	62.1 ± 11.0	73.1 ± 18.1	96.0 ± 28.1
Differental leukocyte count (%)				
Neutrophil	22.4 ± 2.6	24.6 ± 11.5	21.1 ± 7.2	20.8 ± 7.9
Eosinophil	1.9 ± 0.5	1.5 ± 0.5	1.6 ± 0.3	1.8 ± 0.5
Basophil	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0
Monocyte	4.7 ± 1.3	3.5 ± 0.9	3.6 ± 1.2	3.6 ± 0.7
Lymphocyte	70.9 ± 3.0	70.4 ± 12.0	73.7 ± 6.4	73.7 ± 8.2
Reticulocyte count (%)	3.24 ± 0.81	2.92 ± 0.63	3.09 ± 0.49	3.40 ± 1.02

Each value shows mean±S.D.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 25-2. Hematological findings of male rats at the end of the recovery period

Group	Control (vehicle: water for injection)	SF (150/75 mg/kg)
Number of males	5	5
RBC ($\times 10^4/\mu L$)	775 ± 30	782 ± 14
Hemoglobin (g/dL)	14.0 ± 0.3	14.3 ± 0.2
Hematocrit (%)	40.9 ± 1.2	43.1 ± 0.7 **
MCV (fL)	52.8 ± 0.9	55.1 ± 1.6 *
MCH (pg)	18.1 ± 0.6	18.3 ± 0.5
MCHC (g/dL)	34.2 ± 0.7	33.1 ± 0.3 *
Platelet ($\times 10^4/\mu L$)	92.8 ± 18.9	97.3 ± 11.1
PT (sec)	16.2 ± 2.3	19.0 ± 3.9
APTT (sec)	24.6 ± 3.2	27.9 ± 2.8
WBC ($\times 10^2/\mu L$)	95.6 ± 24.4	75.6 ± 9.4
Differental leukocyte count (%)		
Neutrophil	14.5 ± 2.9	16.0 ± 6.8
Eosinophil	1.9 ± 0.4	1.5 ± 0.4
Basophil	0.0 ± 0.1	0.0 ± 0.0
Monocyte	3.9 ± 0.4	3.4 ± 0.8
Lymphocyte	79.7 ± 3.1	79.0 ± 7.7
Reticulocyte count (%)	3.61 ± 0.93	2.62 ± 0.37

Each value shows mean±S.D.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 26-1. Hematological findings of female rats at the end of the dosing period

Group	Control (vehicle: water for injection)	SF (15 mg/kg)	SF (50 mg/kg)	SF (150/75 mg/kg)
Number of females	5	5	5	5
RBC ($\times 10^4/\mu L$)	657 ± 85	699 ± 46	677 ± 31	687 ± 60
Hemoglobin (g/dL)	13.4 ± 1.4	13.4 ± 0.8	13.3 ± 0.6	13.2 ± 0.9
Hematocrit (%)	40.4 ± 3.2	40.3 ± 1.6	40.2 ± 1.7	39.9 ± 2.3
MCV (fL)	61.8 ± 4.1	57.8 ± 2.7	59.5 ± 2.3	58.1 ± 2.5
MCH (pg)	20.5 ± 0.9	19.2 ± 1.0	19.7 ± 0.7	19.2 ± 0.5
MCHC (g/dL)	33.2 ± 0.9	33.2 ± 0.7	33.1 ± 0.3	33.1 ± 0.6
Platelet ($\times 10^4/\mu L$)	128.2 ± 20.9	111.8 ± 13.0	123.4 ± 27.3	115.7 ± 7.3
PT (sec)	12.8 ± 0.3	12.6 ± 0.6	12.9 ± 0.2	12.2 ± 0.7
APTT (sec)	20.2 ± 1.9	19.1 ± 1.1	20.4 ± 0.9	19.9 ± 1.4
WBC ($\times 10^2/\mu L$)	87.1 ± 20.3	103.1 ± 30.9	82.7 ± 37.1	92.7 ± 25.5
Differental leukocyte count (%)				
Neutrophil	24.6 ± 8.4	25.4 ± 9.2	26.3 ± 14.1	34.2 ± 16.7
Eosinophil	0.7 ± 0.5	1.0 ± 0.5	0.9 ± 0.5	1.3 ± 0.4
Basophil	0.0 ± 0.0	0.0 ± 0.1	0.0 ± 0.0	0.0 ± 0.0
Monocyte	3.9 ± 0.4	4.0 ± 1.1	4.0 ± 0.8	4.0 ± 0.7
Lymphocyte	70.8 ± 9.1	69.5 ± 10.1	68.8 ± 14.2	60.5 ± 17.2
Reticulocyte count (%)	11.08 ± 5.45	6.96 ± 0.89	7.35 ± 2.13	6.55 ± 1.20

Each value shows mean±S.D.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 26-2. Hematological findings of female rats at the end of the dosing period, satellite group

Group	Control (vehicle: water for injection)	SF (150/75 mg/kg)
Number of females	5	3
RBC ($\times 10^4/\mu L$)	785 ± 22	759 ± 48
Hemoglobin (g/dL)	14.8 ± 0.4	14.5 ± 0.9
Hematocrit (%)	41.8 ± 1.3	41.4 ± 2.3
MCV (fL)	53.2 ± 0.7	54.6 ± 0.6 *
MCH (pg)	18.8 ± 0.2	19.2 ± 0.2 *
MCHC (g/dL)	35.4 ± 0.6	35.1 ± 0.3
Platelet ($\times 10^4/\mu L$)	105.9 ± 10.6	114.8 ± 24.3
PT (sec)	11.5 ± 0.4	11.7 ± 0.4
APTT (sec)	19.1 ± 1.1	19.1 ± 3.4
WBC ($\times 10^2/\mu L$)	71.4 ± 27.5	68.7 ± 13.2
Differental leukocyte count (%)		
Neutrophil	12.3 ± 3.8	6.9 ± 2.2
Eosinophil	1.3 ± 0.6	1.9 ± 0.4
Basophil	0.0 ± 0.0	0.0 ± 0.1
Monocyte	2.4 ± 0.4	2.5 ± 0.9
Lymphocyte	84.0 ± 3.6	88.6 ± 3.2
Reticulocyte count (%)	3.03 ± 0.46	2.92 ± 0.26

Each value shows mean±S.D.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 26-3. Hematological findings of female rats at the end of the recovery period

Group	Control (vehicle: water for injectio)	SF (150/75 mg/kg)
Number of females	5	3
RBC ($\times 10^4/\mu L$)	747 ± 65	747 ± 111
Hemoglobin (g/dL)	14.0 ± 1.1	14.0 ± 2.0
Hematocrit (%)	41.4 ± 2.9	41.0 ± 2.7
MCV (fL)	55.5 ± 1.5	55.4 ± 5.2
MCH (pg)	18.7 ± 0.3	18.8 ± 0.7
MCHC (g/dL)	33.7 ± 0.7	34.1 ± 2.7
Platelet ($\times 10^4/\mu L$)	89.8 ± 6.3	68.8 ± 0.0
PT (sec)	12.1 ± 0.3	11.9 ± 0.4
APTT (sec)	22.6 ± 2.0	19.1 ± 0.5 *
WBC ($\times 10^2/\mu L$)	38.3 ± 10.9	48.4 ± 5.5
Differental leukocyte count (%)		
Neutrophil	18.1 ± 5.6	17.1 ± 2.4
Eosinophil	2.7 ± 0.7	2.1 ± 0.9
Basophil	0.0 ± 0.0	0.0 ± 0.0
Monocyte	4.2 ± 1.1	3.3 ± 0.7
Lymphocyte	75.0 ± 6.8	77.5 ± 2.1
Reticulocyte count (%)	3.03 ± 0.46	2.38 ± 0.32

Each value shows mean±S.D.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 27-1. Biochemical findings of male rats at the end of the dosing period

Group		Control (vehicle: water for injection)	SF 15 mg/kg	SF 50 mg/kg		SF 150/75 mg/kg	
Number of males		5	5	5		5	
Total protein	g/dL	5.6 ± 0.2	5.4 ± 0.2	5.2 ± 0.2	**	5.3 ± 0.3	*
Albumin	g/dL	3.6 ± 0.1	3.4 ± 0.1	3.4 ± 0.1		3.5 ± 0.2	
A/G		1.72 ± 0.15	1.79 ± 0.3	2.01 ± 0.18		2.03 ± 0.2	
Glucose	mg/dL	131 ± 5	121 ± 11	124 ± 11		135 ± 17	
Total cholesterol	mg/dL	47 ± 10	45 ± 11	49 ± 15		45 ± 11	
Triglyceride	mg/dL	26 ± 4	23 ± 6	30 ± 18		32 ± 23	
Phospholipid	mg/dL	79 ± 12	77 ± 11	81 ± 16		77 ± 18	
AST	U/L	62 ± 7	72 ± 5	71 ± 12		70 ± 16	
ALT	U/L	28 ± 4	34 ± 5	32 ± 10		34 ± 6	
γ-GTP	U/L	0 ± 0	0 ± 0	0 ± 0		0 ± 0	
LDH	U/L	189 ± 131	80 ± 30	123 ± 54		188 ± 131	
Bile acid	μmol/L	10.3 ± 4.3	11.3 ± 5.8	9.2 ± 5.0		10.5 ± 5.3	
BUN	mg/dL	18 ± 1	20 ± 3	18 ± 1		18 ± 3	
Creatinine	mg/dL	0.5 ± 0.1	0.5 ± 0	0.5 ± 0.1		0.5 ± 0.1	
Total bilirubin	mg/dL	0.05 ± 0	0.05 ± 0.01	0.07 ± 0.02		0.07 ± 0.01	
ALP	U/L	322 ± 63	325 ± 54	386 ± 87		345 ± 68	
Inorganic phosphorus	mg/dL	6 ± 0.2	5.8 ± 0.6	6.5 ± 1		6.2 ± 0.4	
Ca	mg/dL	9.5 ± 0.2	9.1 ± 0.2	9.1 ± 0.3		9.3 ± 0.3	
Na	mEq/L	143.4 ± 0.8	143.8 ± 0.4	143.9 ± 0.5		143.6 ± 0.8	
K	mEq/L	4.08 ± 0.24	3.95 ± 0.25	4.05 ± 0.32		3.89 ± 0.22	
Cl	mEq/L	107.4 ± 0.9	107.8 ± 1.2	107.4 ± 1.3		108 ± 1.4	

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 27-2. Biochemical findings of male rats at the end of the recovery period

Group		Control (vehicle: water for injection)	SF 150/75 mg/kg
Number of males		5	5
Total protein	g/dL	5.5 ± 0.2	5.5 ± 0.2
Albumin	g/dL	3.6 ± 0.1	3.5 ± 0.1
A/G		1.92 ± 0.14	1.82 ± 0.12
Glucose	mg/dL	138 ± 10	164 ± 25
Total cholesterol	mg/dL	61 ± 19	48 ± 10
Triglyceride	mg/dL	23 ± 13	23 ± 8
Phospholipid	mg/dL	89 ± 20	78 ± 10
AST	U/L	69 ± 12	66 ± 6
ALT	U/L	31 ± 7	26 ± 4
γ-GTP	U/L	0 ± 0	0 ± 0
LDH	U/L	143 ± 87	198 ± 64
Bile acid	μmol/L	24.0 ± 20.3	12.1 ± 3.7
BUN	mg/dL	15 ± 0	15 ± 2
Creatinine	mg/dL	0.5 ± 0.1	0.5 ± 0
Total bilirubin	mg/dL	0.07 ± 0.01	0.06 ± 0.01
ALP	U/L	289 ± 62	302 ± 45
Inorganic phosphorus	mg/dL	5.8 ± 0.8	6.5 ± 0.5
Ca	mg/dL	9.3 ± 0.3	9.3 ± 0.2
Na	mEq/L	143 ± 0.8	144 ± 1
K	mEq/L	3.69 ± 0.21	3.73 ± 0.21
Cl	mEq/L	106.4 ± 1.3	107.2 ± 1

Each value shows mean ± S.D.

Figures in parentheses indicate number of males.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 28-1. Biochemical findings of female rats at the end of the dosing period

Group		Control (vehicle: water for injection)	SF 15 mg/kg	SF 50 mg/kg	SF 150/75 mg/kg	
Number of females		5	5	5	5	
Total protein	g/dL	5.8 ± 0.2	5.7 ± 0.3	5.6 ± 0.2	5.9 ± 0.3	
Albumin	g/dL	3.9 ± 0.2	3.9 ± 0.2	3.8 ± 0	4 ± 0.2	
A/G		2.08 ± 0.21	2.21 ± 0.14	2.07 ± 0.21	2.2 ± 0.16	
Glucose	mg/dL	119 ± 12	120 ± 7	110 ± 16	114 ± 10	
Total cholesterol	mg/dL	50 ± 10	44 ± 14	49 ± 8	55 ± 13	
Triglyceride	mg/dL	24 ± 7	26 ± 22	25 ± 12	22 ± 6	
Phospholipid	mg/dL	97 ± 18	91 ± 21	101 ± 13	111 ± 20	
AST	U/L	76 ± 11	90 ± 13	76 ± 9	105 ± 29	*
ALT	U/L	40 ± 5	41 ± 6	41 ± 10	45 ± 11	
γ-GTP	U/L	0 ± 0	0 ± 0	0 ± 0	0 ± 0	
LDH	U/L	124 ± 121	103 ± 62	89 ± 53	143 ± 102	
Bile acid	μmol/L	14.7 ± 7.6	14.3 ± 5.4	19.1 ± 14.5	14.1 ± 3.2	
BUN	mg/dL	18 ± 3	18 ± 2	18 ± 2	19 ± 3	
Creatinine	mg/dL	0.6 ± 0.1	0.6 ± 0.1	0.6 ± 0	0.6 ± 0.1	
Total bilirubin	mg/dL	0.08 ± 0.02	0.07 ± 0.02	0.07 ± 0.02	0.07 ± 0.01	
ALP	U/L	166 ± 11	195 ± 104	178 ± 22	242 ± 35	*
Inorganic phosphorus	mg/dL	6.5 ± 0.7	6.8 ± 0.4	7.3 ± 1.1	7.5 ± 1.3	
Ca	mg/dL	9.5 ± 0.3	9.5 ± 0.3	9.5 ± 0.3	9.7 ± 0.2	
Na	mEq/L	141.4 ± 0.7	140.5 ± 1.4	141.1 ± 0.6	142.2 ± 1.7	
K	mEq/L	3.96 ± 0.12	3.7 ± 0.3	4.27 ± 0.85	3.71 ± 0.29	
Cl	mEq/L	107.6 ± 1.7	106.7 ± 1.9	107.4 ± 0.9	107.9 ± 0.7	

Each value shows mean ± S.D.

Figures in parentheses indicate number of females.

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 28-2. Biochemical findings of female rats at the end of the dosing period, satellite group

Group		Control (vehicle: water for injection)	SF 150/75 mg/kg	
Number of females		5	3	
Total protein	g/dL	6.3 ± 0.4	5.9 ± 0.7	
Albumin	g/dL	4.4 ± 0.4	4 ± 0.5	
A/G		2.21 ± 0.28	2.1 ± 0.07	
Glucose	mg/dL	121 ± 20	126 ± 31	
Total cholesterol	mg/dL	66 ± 8	81 ± 6	*
Triglyceride	mg/dL	15 ± 9	16 ± 10	
Phospholipid	mg/dL	123 ± 17	138 ± 11	
AST	U/L	76 ± 18	78 ± 13	
ALT	U/L	29 ± 16	28 ± 2	
γ-GTP	U/L	0 ± 0	0 ± 0	
LDH	U/L	115 ± 46	238 ± 252	
Bile acid	μmol/L	16.4 ± 5.3	10.0 ± 1.1	
BUN	mg/dL	19 ± 3	17 ± 1	
Creatinine	mg/dL	0.7 ± 0	0.7 ± 0.1	
Total bilirubin	mg/dL	0.09 ± 0.02	0.08 ± 0.01	
ALP	U/L	155 ± 31	219 ± 36	*
Inorganic phosphorus	mg/dL	5.1 ± 0.7	6.3 ± 1.9	
Ca	mg/dL	9.6 ± 0.4	9.6 ± 0.9	
Na	mEq/L	142.5 ± 0.9	142.1 ± 0.7	
K	mEq/L	3.91 ± 0.35	5.63 ± 3.24	
Cl	mEq/L	106.9 ± 1.0	105.8 ± 2.0	

Each value shows mean ± S.D.
Figures in parentheses indicate number of females.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 28-3. Biochemical findings of female rats at the end of the recovery period

Group		Control (vehicle: water for injection)	SF 150/75 mg/kg	
Number of females		5	3	
Total protein	g/dL	5.8 ± 0.4	5.9 ± 0.1	
Albumin	g/dL	4 ± 0.3	3.9 ± 0.2	
A/G		2.29 ± 0.12	1.97 ± 0.28	
Glucose	mg/dL	133 ± 6	119 ± 19	
Total cholesterol	mg/dL	60 ± 7	71 ± 15	
Triglyceride	mg/dL	15 ± 8	17 ± 7	
Phospholipid	mg/dL	110 ± 11	121 ± 18	
AST	U/L	60 ± 8	57 ± 0	
ALT	U/L	23 ± 7	18 ± 3	
γ-GTP	U/L	0 ± 0	0 ± 0	
LDH	U/L	68 ± 20	80 ± 40	
Bile acid	μmol/L	9.3 ± 2.0	16.0 ± 5.3	*
BUN	mg/dL	16 ± 2	18 ± 2	
Creatinine	mg/dL	0.7 ± 0.1	0.6 ± 0.2	
Total bilirubin	mg/dL	0.07 ± 0.01	0.08 ± 0.01	
ALP	U/L	151 ± 40	150 ± 26	
Inorganic phosphorus	mg/dL	4 ± 0.5	5 ± 0.9	
Ca	mg/dL	9.1 ± 0.4	9.2 ± 0.4	
Na	mEq/L	142.9 ± 0.7	143.8 ± 0.7	
K	mEq/L	3.64 ± 0.4	3.62 ± 0.09	
Cl	mEq/L	106.9 ± 1.6	108.5 ± 1.7	

Each value shows mean ± S.D.
Figures in parentheses indicate number of females.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 29-1. Organ weights of male rats at the end of the dosing period

Group		Control (vehicle: water for injection)	SF 15 mg/kg	SF 50 mg/kg	SF 150/75 mg/kg
Number of males		7	12	12	6
Body weight	(g)	453.3 ± 36.5	449.2 ± 33.1	455.7 ± 30.2	451.9 ± 20.2
Brain	(mg)	1975.4 ± 73.7	1983.8 ± 86.4	1979.3 ± 67.2	1982.9 ± 51.0
	(mg/g)	4.381 ± 0.388	4.435 ± 0.322	4.357 ± 0.260	4.395 ± 0.227
Thymus	(mg)	311.3 ± 67.7	291.0 ± 59.0	290.0 ± 65.1	279.7 ± 50.5
	(mg/g)	0.693 ± 0.184	0.645 ± 0.104	0.638 ± 0.149	0.619 ± 0.114
Heart	(mg)	1340.2 ± 108.9	1355.1 ± 115.8	1400.5 ± 107.3	1342.8 ± 199.2
	(mg/g)	2.963 ± 0.215	3.020 ± 0.197	3.074 ± 0.137	2.966 ± 0.371
Liver	(mg)	12137.9 ± 896.2	11159.6 ± 1131.8	11571.4 ± 1279.1	11525.6 ± 1158.7
	(mg/g)	26.815 ± 1.396	24.816 ± 1.230 *	25.347 ± 1.443	25.466 ± 1.716
Kidney (R)	(mg)	1566.7 ± 63.5	1513.4 ± 138.0	1589.4 ± 133.9	1514.7 ± 159.0
	(mg/g)	3.475 ± 0.305	3.382 ± 0.350	3.491 ± 0.217	3.351 ± 0.302
Kidney (L)	(mg)	1576.8 ± 84.0	1496.4 ± 154.2	1574.5 ± 162.0	1529.6 ± 119.7
	(mg/g)	3.495 ± 0.297	3.342 ± 0.359	3.457 ± 0.286	3.388 ± 0.267
Kidneys	(mg)	3143.6 ± 142.9	3009.7 ± 282.2	3163.9 ± 292.2	3044.3 ± 271.4
	(mg/g)	6.970 ± 0.594	6.724 ± 0.689	6.948 ± 0.492	6.738 ± 0.544
Spleen	(mg)	775.4 ± 105.7	752.1 ± 100.1	789.9 ± 131.4	800.3 ± 103.1
	(mg/g)	1.713 ± 0.214	1.675 ± 0.186	1.732 ± 0.253	1.767 ± 0.174
Testis (R)	(mg)	1657.2 ± 107.5	1615.1 ± 86.0	1611.2 ± 142.6	1600.7 ± 89.5
	(mg/g)	3.678 ± 0.401	3.616 ± 0.354	3.547 ± 0.351	3.545 ± 0.203
Testis (L)	(mg)	1645.0 ± 101.2	1622.0 ± 94.0	1628.1 ± 169.1	1573.1 ± 97.4
	(mg/g)	3.656 ± 0.450	3.633 ± 0.389	3.582 ± 0.387	3.483 ± 0.204
Testes	(mg)	3302.2 ± 203.4	3237.1 ± 175.7	3239.3 ± 309.5	3173.7 ± 184.4
	(mg/g)	7.334 ± 0.846	7.249 ± 0.738	7.128 ± 0.732	7.028 ± 0.401
Epididymis (R)	(mg)	658.5 ± 84.1	611.4 ± 40.4	643.7 ± 45.7	592.5 ± 34.7
	(mg/g)	1.455 ± 0.155	1.367 ± 0.116	1.417 ± 0.127	1.313 ± 0.084
Epididymis (L)	(mg)	635.6 ± 24.8	606.4 ± 36.1	634.9 ± 43.1	594.8 ± 29.1
	(mg/g)	1.409 ± 0.106	1.357 ± 0.136	1.399 ± 0.134	1.318 ± 0.076
Epididymides	(mg)	1294.2 ± 100.9	1217.8 ± 71.0	1278.5 ± 84.0	1187.3 ± 62.7
	(mg/g)	2.863 ± 0.223	2.724 ± 0.244	2.816 ± 0.254	2.630 ± 0.158
Prostate, ventral	(mg)	644.7 ± 104.7	609.6 ± 132.4	648.1 ± 132.8	597.0 ± 137.0
	(mg/g)	1.419 ± 0.168	1.361 ± 0.289	1.427 ± 0.307	1.322 ± 0.309
Seminal vesicles	(mg)	1698.6 ± 267.6	1809.1 ± 253.3	1883.6 ± 220.7	1532.5 ± 161.7
	(mg/g)	3.752 ± 0.524	4.046 ± 0.631	4.152 ± 0.561	3.408 ± 0.500
Thyroid gland	(mg)	20.6 ± 3.1	20.3 ± 2.7	19.8 ± 3.1	21.2 ± 6.7
	(mg/g)	0.046 ± 0.007	0.045 ± 0.005	0.044 ± 0.008	0.047 ± 0.014

Each value shows mean ± S.D.
Figures in parentheses indicate number of males.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 29-1(continued). Organ weights of male rats at the end of the dosing period

Group		Control (vehicle: water for injection)	SF 15 mg/kg	SF 50 mg/kg	SF 150/75 mg/kg
Number of males		7	12	12	6
Body weight	(g)	453.3 ± 36.5	449.2 ± 33.1	455.7 ± 30.2	451.9 ± 20.2
Adrenal gland (R)	(mg)	28.9 ± 4.4	27.5 ± 4.8	27.4 ± 2.9	26.7 ± 4.9
	(mg/g)	0.064 ± 0.006	0.061 ± 0.009	0.061 ± 0.008	0.059 ± 0.009
Adrenal gland (L)	(mg)	28.8 ± 3.5	29.1 ± 4.7	28.6 ± 3.0	29.5 ± 6.1
	(mg/g)	0.064 ± 0.005	0.065 ± 0.009	0.063 ± 0.008	0.065 ± 0.012
Adrenal glands	(mg)	57.7 ± 7.8	56.6 ± 9.5	56.0 ± 5.7	56.2 ± 10.9
	(mg/g)	0.127 ± 0.011	0.126 ± 0.018	0.123 ± 0.015	0.124 ± 0.020

Each value shows mean ± S.D.
Figures in parentheses indicate number of males.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 29-2. Organ weights of male rats at the end of the recovery period

Group		Control (vehicle: water for injection)				SF 150/75 mg/kg		
Number of males		5				5		
Body weight	(g)	479.5	±	33.4		475.2	±	42.8
Brain	(mg)	2056.4	±	72.5		2048.7	±	108.4
	(mg/g)	4.303	±	0.290		4.326	±	0.241
Thymus	(mg)	287.2	±	61.1		253.9	±	88.7
	(mg/g)	0.605	±	0.152		0.532	±	0.169
Heart	(mg)	1448.5	±	35.3		1394.8	±	121.6
	(mg/g)	3.030	±	0.187		2.939	±	0.159
Liver	(mg)	11818.0	±	1136.3		11717.2	±	1409.2
	(mg/g)	24.668	±	2.076		24.624	±	1.484
Kidney (R)	(mg)	1501.2	±	113.7		1503.3	±	142.4
	(mg/g)	3.131	±	0.078		3.173	±	0.290
Kidney (L)	(mg)	1539.3	±	133.8		1507.4	±	147.6
	(mg/g)	3.211	±	0.193		3.180	±	0.273
Kidneys	(mg)	3040.6	±	235.4		3010.7	±	274.4
	(mg/g)	6.342	±	0.245		6.353	±	0.526
Spleen	(mg)	788.7	±	103.2		829.2	±	128.8
	(mg/g)	1.657	±	0.295		1.748	±	0.238
Testis (R)	(mg)	1671.2	±	172.2		1575.1	±	230.6
	(mg/g)	3.514	±	0.563		3.349	±	0.662
Testis (L)	(mg)	1692.2	±	130.3		1550.3	±	240.4
	(mg/g)	3.554	±	0.479		3.300	±	0.696
Testes	(mg)	3363.4	±	301.7		3125.3	±	468.5
	(mg/g)	7.069	±	1.041		6.650	±	1.354
Epididymis (R)	(mg)	657.3	±	71.7		605.3	±	72.9
	(mg/g)	1.382	±	0.223		1.287	±	0.226
Epididymis (L)	(mg)	646.2	±	61.5		621.1	±	69.1
	(mg/g)	1.356	±	0.193		1.323	±	0.245
Epididymides	(mg)	1303.5	±	130.2		1226.3	±	140.0
	(mg/g)	2.738	±	0.412		2.610	±	0.468
Prostate, ventral	(mg)	529.1	±	155.5		673.7	±	104.5
	(mg/g)	1.121	±	0.387		1.429	±	0.257
Seminal vesicles	(mg)	1614.4	±	272.4		1630.3	±	128.0
	(mg/g)	3.355	±	0.378		3.468	±	0.544
Thyroid gland	(mg)	20.7	±	1.4		19.4	±	2.0
	(mg/g)	0.044	±	0.005		0.041	±	0.006

Each value shows mean ± S.D.
Figures in parentheses indicate number of males.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 29-2(continued). Organ weights of male rats at the end of the recovery period

Group		Control (vehicle: water for injection)			SF 150/75 mg/kg		
Number of males		5			5		
Body weight	(g)	479.5	±	33.4	475.2	±	42.8
Adrenal gland (R)	(mg)	26.4	±	2.0	27.8	±	2.0
	(mg/g)	0.055	±	0.007	0.059	±	0.005
Adrenal gland (L)	(mg)	27.2	±	2.0	28.3	±	1.7
	(mg/g)	0.057	±	0.006	0.060	±	0.006
Adrenal glands	(mg)	53.6	±	3.6	56.2	±	3.1
	(mg/g)	0.112	±	0.013	0.119	±	0.010

Each value shows mean ± S.D.
Figures in parentheses indicate number of males.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 30-1. Organ weights of female rats at the end of the dosing period

Group		Control (vehicle: water for injection)	SF 15 mg/kg	SF 50 mg/kg	SF 150/75 mg/kg
Number of females		11	12	12	11
Body weight	(g)	288.2 ± 17.4	289.6 ± 18.8	298.6 ± 22.1	281.3 ± 13.0
Brain	(mg)	1877.6 ± 47.6	1894.8 ± 55.0	1862.8 ± 45.5	1864.0 ± 58.3
	(mg/g)	6.536 ± 0.416	6.563 ± 0.367	6.268 ± 0.467	6.639 ± 0.357
Thymus	(mg)	193.7 ± 47.2	202.9 ± 47.9	204.2 ± 58.2	175.3 ± 62.7
	(mg/g)	0.669 ± 0.137	0.699 ± 0.150	0.687 ± 0.200	0.619 ± 0.214
Heart	(mg)	991.4 ± 102.8	959.2 ± 71.9	966.5 ± 58.0	964.0 ± 118.0
	(mg/g)	3.434 ± 0.180	3.313 ± 0.159	3.245 ± 0.201	3.427 ± 0.388
Liver	(mg)	9401.3 ± 668.8	9445.6 ± 467.5	9711.5 ± 912.3	9576.3 ± 712.4
	(mg/g)	32.631 ± 1.598	32.692 ± 1.853	32.625 ± 3.448	34.022 ± 1.475
Kidney (R)	(mg)	984.2 ± 86.4	1000.5 ± 61.8	1025.4 ± 98.5	1013.2 ± 94.0
	(mg/g)	3.419 ± 0.272	3.463 ± 0.247	3.440 ± 0.314	3.603 ± 0.307
Kidney (L)	(mg)	975.1 ± 88.9	991.9 ± 63.5	1002.0 ± 68.1	1008.5 ± 82.9
	(mg/g)	3.382 ± 0.219	3.434 ± 0.248	3.366 ± 0.266	3.588 ± 0.279
Kidneys	(mg)	1959.3 ± 162.7	1992.4 ± 120.6	2027.3 ± 161.7	2021.7 ± 172.2
	(mg/g)	6.800 ± 0.442	6.897 ± 0.481	6.807 ± 0.557	7.191 ± 0.567
Spleen	(mg)	708.6 ± 151.7	711.7 ± 124.6	686.6 ± 89.6	671.0 ± 85.3
	(mg/g)	2.460 ± 0.513	2.467 ± 0.460	2.310 ± 0.335	2.385 ± 0.269
Ovary (R)	(mg)	53.4 ± 8.5	49.4 ± 6.0	53.7 ± 10.0	51.0 ± 8.5
	(mg/g)	0.185 ± 0.027	0.171 ± 0.025	0.181 ± 0.036	0.182 ± 0.033
Ovary (L)	(mg)	48.1 ± 8.1	53.1 ± 9.7	49.3 ± 7.1	51.7 ± 4.8
	(mg/g)	0.167 ± 0.024	0.185 ± 0.041	0.166 ± 0.027	0.184 ± 0.019
Ovaries	(mg)	101.5 ± 12.9	102.5 ± 13.5	103.1 ± 11.6	102.7 ± 8.9
	(mg/g)	0.352 ± 0.036	0.356 ± 0.058	0.347 ± 0.048	0.366 ± 0.039
Uterus	(mg)	631.5 ± 78.7	594.8 ± 133.7	613.0 ± 66.3	562.8 ± 98.3
	(mg/g)	2.190 ± 0.232	2.050 ± 0.415	2.062 ± 0.262	2.002 ± 0.355
Thyroid gland	(mg)	15.7 ± 4.3	13.9 ± 2.4	14.5 ± 2.9	13.9 ± 2.8
	(mg/g)	0.055 ± 0.015	0.048 ± 0.009	0.049 ± 0.011	0.049 ± 0.010
Adrenal gland (R)	(mg)	35.4 ± 4.4	35.8 ± 6.4	37.0 ± 2.4	39.9 ± 3.9
	(mg/g)	0.123 ± 0.015	0.123 ± 0.020	0.125 ± 0.010	0.142 ± 0.014 *
Adrenal gland (L)	(mg)	37.3 ± 4.5	37.7 ± 5.0	38.0 ± 3.1	40.0 ± 3.6
	(mg/g)	0.130 ± 0.014	0.131 ± 0.020	0.128 ± 0.016	0.142 ± 0.014
Adrenal glands	(mg)	72.7 ± 8.6	73.5 ± 11.2	75.0 ± 4.6	79.9 ± 7.2
	(mg/g)	0.253 ± 0.028	0.254 ± 0.039	0.253 ± 0.024	0.285 ± 0.028 *

Each value shows mean ± S.D.
Figures in parentheses indicate number of males.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 30-2. Organ weights of female rats at the end of the dosing period, satellite group

Group		Control (vehicle: water for injection)			SF 150/75 mg/kg		
Number of females		5			3		
Body weight	(g)	259.5	±	16.1	248.7	±	14.7
Brain	(mg)	1831.9	±	41.0	1875.0	±	64.2
	(mg/g)	7.079	±	0.446	7.549	±	0.332
Thymus	(mg)	311.2	±	54.7	267.2	±	130.7
	(mg/g)	1.196	±	0.173	1.098	±	0.608
Heart	(mg)	849.4	±	64.6	792.2	±	36.8
	(mg/g)	3.272	±	0.119	3.187	±	0.094
Liver	(mg)	6620.0	±	586.6	7185.8	±	925.2
	(mg/g)	25.534	±	2.040	28.836	±	2.583
Kidney (R)	(mg)	901.3	±	22.5	934.3	±	125.7
	(mg/g)	3.485	±	0.250	3.753	±	0.410
Kidney (L)	(mg)	875.5	±	22.3	913.9	±	94.0
	(mg/g)	3.386	±	0.270	3.678	±	0.370
Kidneys	(mg)	1776.7	±	43.4	1848.1	±	216.3
	(mg/g)	6.871	±	0.518	7.431	±	0.755
Spleen	(mg)	557.9	±	30.2	537.0	±	95.2
	(mg/g)	2.154	±	0.130	2.150	±	0.268
Ovary (R)	(mg)	43.6	±	9.9	53.5	±	3.4
	(mg/g)	0.167	±	0.030	0.216	±	0.025
Ovary (L)	(mg)	45.2	±	8.1	45.3	±	9.6
	(mg/g)	0.173	±	0.023	0.183	±	0.040
Ovaries	(mg)	88.8	±	16.1	98.8	±	12.4
	(mg/g)	0.340	±	0.042	0.399	±	0.059
Uterus	(mg)	567.1	±	142.4	548.2	±	60.4
	(mg/g)	2.208	±	0.657	2.215	±	0.349
Thyroid gland	(mg)	14.9	±	3.5	14.2	±	1.1
	(mg/g)	0.057	±	0.010	0.057	±	0.005
Adrenal gland (R)	(mg)	32.4	±	3.4	27.4	±	2.3
	(mg/g)	0.125	±	0.017	0.110	±	0.012
Adrenal gland (L)	(mg)	34.1	±	3.1	30.8	±	1.1
	(mg/g)	0.132	±	0.017	0.124	±	0.008
Adrenal glands	(mg)	66.5	±	6.2	58.2	±	3.4
	(mg/g)	0.257	±	0.033	0.235	±	0.020

Each value shows mean ± S.D.
Figures in parentheses indicate number of males.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 30-3. Organ weights of female rats at the end of the recovery period

Group		Control (vehicle: water for injection)			SF 150/75 mg/kg		
Number of females		5			3		
Body weight	(g)	276.3	±	22.7	265.5	±	10.3
Brain	(mg)	1821.8	±	60.1	1870.7	±	47.0
	(mg/g)	6.621	±	0.447	7.051	±	0.258
Thymus	(mg)	263.6	±	49.6	209.2	±	80.8
	(mg/g)	0.951	±	0.130	0.793	±	0.317
Heart	(mg)	898.3	±	96.4	962.7	±	118.2
	(mg/g)	3.252	±	0.237	3.628	±	0.454
Liver	(mg)	7164.7	±	693.8	6645.1	±	216.9
	(mg/g)	25.915	±	0.898	25.035	±	0.419
Kidney (R)	(mg)	947.0	±	65.6	894.5	±	61.1
	(mg/g)	3.442	±	0.308	3.367	±	0.112
Kidney (L)	(mg)	901.9	±	45.5	871.8	±	33.1
	(mg/g)	3.278	±	0.266	3.284	±	0.022
Kidneys	(mg)	1848.9	±	108.8	1766.3	±	93.9
	(mg/g)	6.720	±	0.566	6.650	±	0.124
Spleen	(mg)	573.7	±	54.3	527.7	±	67.8
	(mg/g)	2.082	±	0.197	1.983	±	0.177
Ovary (R)	(mg)	47.2	±	10.1	35.9	±	13.5
	(mg/g)	0.170	±	0.028	0.134	±	0.046
Ovary (L)	(mg)	46.5	±	8.5	38.1	±	9.6
	(mg/g)	0.167	±	0.023	0.143	±	0.032
Ovaries	(mg)	93.7	±	18.2	74.0	±	23.1
	(mg/g)	0.337	±	0.049	0.277	±	0.077
Uterus	(mg)	525.1	±	36.9	641.7	±	371.6
	(mg/g)	1.909	±	0.171	2.388	±	1.292
Thyroid gland	(mg)	20.8	±	8.1	16.1	±	1.3
	(mg/g)	0.075	±	0.029	0.061	±	0.007
Adrenal gland (R)	(mg)	35.3	±	5.9	27.8	±	3.8
	(mg/g)	0.129	±	0.024	0.105	±	0.018
Adrenal gland (L)	(mg)	37.5	±	7.8	29.9	±	5.6
	(mg/g)	0.137	±	0.032	0.113	±	0.025
Adrenal glands	(mg)	72.8	±	13.7	57.6	±	9.4
	(mg/g)	0.265	±	0.056	0.218	±	0.043

Each value shows mean ± S.D.
Figures in parentheses indicate number of males.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 31-1. Macroscopic findings of male rats at the end of the dosing period

Group	Control (Vehicle)		SF 15 mg/kg		SF 50 mg/kg		SF 150/75 mg/kg	
Findings / Grade	-	P	-	P	-	P	-	P
Epididymis								
Nodule, yellowish white, caudal, unilateral	6	1	11	1	12	0	6	0
Kidney								
Pale colored area, unilateral	7	0	12	0	12	0	5	1
Whitish area, single/scattered, uni-/bilateral	6	1	12	0	12	0	5	1
Liver								
Whitish area	7	0	12	0	11	1	6	0
Small intestine								
Diverticulum, between the jejunum and ileum	7	0	12	0	11	1	6	0
Tooth								
Discoloration, whitish, surface, maxillary/mandibular incisor	7	0	12	0	12	0	4	2

Notes) - : No abnormal changes P : Non-graded change
Numerals represent the number of animals.
Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 31-2. Macroscopic findings of male rats at the end of the recovery period

Group	Control (Vehicle)		SF 150/75 mg/kg	
Findings / Grade	-	P	-	P
Tooth				
Fracture, maxillary incisor	5	0	4	1
Loss, unilateral, maxillary incisor	5	0	4	1

Notes) - : No abnormal changes P : Non-graded change

Numerals represent the number of animals.

Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 32-1. Macroscopic findings of female rats at the end of the dosing period

Group	Control (Vehicle)		SF 15 mg/kg		SF 50 mg/kg		SF 150/75 mg/kg	
Findings / Grade	-	P	-	P	-	P	-	P
Kidney								
Whitish area, scattered, bilateral	11	0	12	0	12	0	10	1
Liver								
Diaphragmatic nodule	11	0	11	1	12	0	11	0
Thymus								
Small	11	0	12	0	12	0	10	1
Tooth								
Discoloration, whitish, surface, maxillary/mandibular incisor	11	0	12	0	12	0	9	2

Notes) - : No abnormal changes P : Non-graded change

Numerals represent the number of animals.

Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 32-2. Macroscopic findings of female rats at the end of the dosing period, satellite group

Group	Control (Vehicle)		SF 150/75 mg/kg	
Findings / Grade	-	P	-	P
Tooth				
Discoloration, whitish, surface, maxillary/mandibular incisor	5	0	1	2

Notes) - : No abnormal changes P : Non-graded change

Numerals represent the number of animals.

Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 32-3. Macroscopic findings of female rats at the end of the recovery period

Group	Control (Vehicle)		SF 150/75 mg/kg	
Findings / Grade	-	P	-	P
Heart				
Discoloration, pale colored	5	0	2	1
Tooth				
Malocclusion	5	0	2	1

Notes) - : No abnormal changes P : Non-graded change
Numerals represent the number of animals.
Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 33-1. Histopathological findings of male rats at the end of the dosing period

Group	Control (Vehicle)							SF 15 mg/kg							SF 50 mg/kg							SF 150/75 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain	5						2	0						12	0						12	5						1
Spinal cord	5						2	0						12	0						12	5						1
Pituitary gland																												
Remnant, Rathke's pouch	3					2	2	0					0	12	0					0	12	5					0	1
Submandibular gland	5						2	0						12	0						12	5						1
Sublingual gland	5						2	0						12	0						12	5						1
Lymph node, submandibular	5						2	0						12	0						12	5						1
Thyroid gland																												
Ectopic thymic tissue	5					0	2	0					0	12	0					0	12	4					1	1
Ultimobranchial body	5					0	2	0					0	12	0					0	12	3					2	1
Parathyroid gland	5						2	0						12	0						12	5						1
Thymus	5						2	0						12	0						12	5						1
Heart																												
Degeneration/fibrosis, myocardial, focal	5	0	0	0	0		2	2	3	0	0	0		2	3	2	0	0	0		2	5	0	0	0	0		1
Trachea	5						2	0						12	0						12	5						1
Lung																												
Accumulation, foam cell, alveolus	4	1	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	5	0	0	0	0		1
Metaplasia, osseous, focal	5	0	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	1	0	0	0		1
Bronchus	5						2	0						12	0						12	5						1

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined
Numerals represent the number of animals.
Vehicle: water for injection
*P<0.05, **P<0.01 : Significantly different from control (Mann-Whitney U test).
#P<0.05, ##P<0.01 : Significantly different from control (Fisher's exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 33-1(continued). Histopathological findings of male rats at the end of the dosing period

Group	Control (Vehicle)							SF 15 mg/kg							SF 50 mg/kg							SF 150/75 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver																												
Fatty change, hepatocyte, periportal	2	3	0	0	0		2	0	0	0	0	0		12	0	1	0	0	0		11	3	2	0	0	0		1
Foci/area, cellular alteration, vacuolated cell	5	0	0	0	0		2	0	0	0	0	0		12	0	1	0	0	0		11	5	0	0	0	0		1
Microgranuloma	2	3	0	0	0		2	0	0	0	0	0		12	1	0	0	0	0		11	3	2	0	0	0		1
Pancreas																												
Hyperplasia, duct	5	0	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	4	1	0	0	0		1
Stomach																												
Accumulation, lymphocyte, submucosa, glandular stomach	5	0	0	0	0		2	5	0	0	0	0		7	2	2	1	0	0		7	2	2	1	0	0		1
Cellular infiltration, eosinophil, lamina muscularis mucosa/submucosa, glandular stomach	0	4	1	0	0		2	0	1	3	1	0		7	0	0	0	5	0		7 **	0	0	2	3	0		1 *
Dendritic-like cell, increased, limiting ridge, mucosa	4	1	0	0	0		2	1	2	2	0	0		7	0	1	3	1	0		7 *,#	0	0	5	0	0		1 **,#
Duodenum	5						2	0						12	0						12	5						1
Jejunum	5						2	0						12	0						12	5						1
Ileum																												
Diverticulum	5					0	2	0					0	12	0					1	11	5					0	1
Cecum	5						2	0						12	0						12	5						1
Colon	5						2	0						12	0						12	5						1
Rectum	5						2	0						12	0						12	5						1
Lymph node, mesenteric	5						2	0						12	0						12	5						1
Spleen																												
Deposit, pigment, brown	0	0	0	5	0		2	0	0	0	0	0		12	0	0	0	0	0		12	0	0	0	5	0		1
Hematopoiesis, extramedullary	0	1	1	3	0		2	0	0	0	0	0		12	0	0	0	0	0		12	0	4	1	0	0		1

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined
Numerals represent the number of animals.
Vehicle: water for injection
*P<0.05, **P<0.01 : Significantly different from control (Mann-Whitney U test).
#P<0.05, ##P<0.01 : Significantly different from control (Fisher's exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 33-1(continued). Histopathological findings of male rats at the end of the dosing period

Group	Control (Vehicle)							SF 15 mg/kg							SF 50 mg/kg							SF 150/75 mg/kg							
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	
Kidney																													
Basophilic tubule, cortex	1	4	0	0	0		2	3	2	0	0	0		7	2	3	0	0	0		7	2	3	1	0	0			
Cellular infiltration, lymphocyte, interstitial	5	0	0	0	0		2	4	1	0	0	0		7	4	1	0	0	0		7	4	1	1	0	0			
Cyst, medulla	4					1	2	4					1	7	5					0	7	6					0		
Dilatation, lumen, distal tubule	5	0	0	0	0		2	5	0	0	0	0		7	5	0	0	0	0		7	5	1	0	0	0			
Mineralization, cortex	5	0	0	0	0		2	5	0	0	0	0		7	5	0	0	0	0		7	3	3	0	0	0			
Nephroblastoma	5					0	2	5					0	7	5					0	7	5					1		
Urinary bladder	5						2	0						12	0						12	5						1	
Adrenal gland																													
Vacuolation, cytoplasmic, zona fasciculata	4	1	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	5	0	0	0	0		1	
Testis	5						2	0						12	0						12	5						1	
Epididymis																													
Granuloma, spermatic, unilateral	4					1	2	0					1	11	0					0	12	5					0	1	
Prostate																													
Cellular infiltration, lymphocyte, interstitial	3	2	0	0	0		2	0	0	0	0	0		12	0	0	0	0	0		12	3	2	0	0	0		1	
Seminal vesicle	5						2	0						12	0						12	5						1	
Coagulating gland	5						2	0						12	0						12	5						1	
Eyeball	5						2	0						12	0						12	5						1	
Harderian gland	5						2	0						12	0						12	5						1	
Sciatic nerve	5						2	0						12	0						12	5						1	
Skeletal muscle	5						2	0						12	0						12	5						1	
Femur																													
Deposit, basophilic substance, epiphysis/growth plate/metaphysis	5	0	0	0	0		2	5	0	0	0	0		7	5	0	0	0	0		7	0	0	0	5	0		1	**, ##
Marrow, femur	5						2	0						12	0						12	5						1	

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined
Numerals represent the number of animals.
Vehicle: water for injection
*P<0.05, **P<0.01 : Significantly different from control (Mann-Whitney U test).
#P<0.05, ##P<0.01 : Significantly different from control (Fisher's exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 33-2. Histopathological findings of male rats at the end of the recovery period

Group	Control (Vehicle)							SF 150/75 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain	0						5	0						5
Spinal cord	0						5	0						5
Pituitary gland	0						5	0						5
Submandibular gland	0						5	0						5
Sublingual gland	0						5	0						5
Lymph node, submandibular	0						5	0						5
Thyroid gland	0						5	0						5
Parathyroid gland	0						5	0						5
Thymus	0						5	0						5
Heart														
Degeneration/fibrosis, myocardial, focal	4	1	0	0	0			3	2	0	0	0		
Trachea	0						5	0						5
Lung	0						5	0						5
Bronchus	0						5	0						5

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined
Numerals represent the number of animals.
Vehicle: water for injection
Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 33-2(continued). Histopathological findings of male rats at the end of the recovery period

Group	Control (Vehicle)							SF 150/75 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver	0						5	0						5
Pancreas	0						5	0						5
Stomach														
Accumulation, lymphocyte, submucosa, glandular stomach	5	0	0	0	0			4	1	0	0	0		
Cellular infiltration, eosinophil, lamina muscularis mucosa/submucosa, glandular stomach	0	4	1	0	0			0	5	0	0	0		
Dendritic-like cell, increased, limiting ridge, mucosa	4	0	1	0	0			1	3	1	0	0		
Duodenum	0						5	0						5
Jejunum	0						5	0						5
Ileum	0						5	0						5
Cecum	0						5	0						5
Colon	0						5	0						5
Rectum	0						5	0						5
Lymph node, mesenteric	0						5	0						5
Spleen	0						5	0						5

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined
Numerals represent the number of animals.
Vehicle: water for injection
Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 33-2(continued). Histopathological findings of male rats at the end of the recovery period

Group	Control (Vehicle)							SF 150/75 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Kidney														
Basophilic tubule, cortex	2	3	0	0	0			1	4	0	0	0		
Cellular infiltration, lymphocyte, interstitial	5	0	0	0	0			3	1	1	0	0		
Urinary bladder	0						5	0						5
Adrenal gland	0						5	0						5
Testis	0						5	0						5
Epididymis	0						5	0						5
Prostate	0						5	0						5
Seminal vesicle	0						5	0						5
Coagulating gland	0						5	0						5
Eyeball	0						5	0						5
Harderian gland	0						5	0						5
Sciatic nerve	0						5	0						5
Skeletal muscle	0						5	0						5
Femur	5							5						
Marrow, femur	0						5	0						5

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined
Numerals represent the number of animals.
Vehicle: water for injection
Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 34-1. Histopathological findings of female rats at the end of the dosing period

Group	Control (Vehicle)							SF 15 mg/kg							SF 50 mg/kg							SF 150/75 mg/kg					
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P
Brain	5						6	0						12	0						12	5					
Spinal cord	5						6	0						12	0						12	5					
Pituitary gland																											
Remnant, Rathke's pouch	5					0	6	0					0	12	0					0	12	4					1
Submandibular gland	5						6	0						12	0						12	5					
Sublingual gland																											
Atrophy, acinus, unilateral	5	0	0	0	0		6	0	0	0	0	0		12	0	0	0	0	0		12	4	0	0	1	0	
Cellular infiltration, mononuclear cell, interstitial, unilateral	5	0	0	0	0		6	0	0	0	0	0		12	0	0	0	0	0		12	4	0	1	0	0	
Lymph node, submandibular	5						6	0						12	0						12	5					
Thyroid gland																											
Ultimobranchial body	3					2	6	0					0	12	0					0	12	3					2
Parathyroid gland	5						6	0						12	0						12	5					
Thymus																											
Atrophy	5	0	0	0	0		6	0	0	0	0	0		12	0	0	0	0	0		12	4	0	0	1	0	
Heart																											
Edema, around an artery	5	0	0	0	0		6	5	0	0	0	0		7	5	0	0	0	0		7	4	0	1	0	0	
Trachea	5						6	0						12	0						12	5					
Lung	5						6	0						12	0						12	5					
Bronchus	5						6	0						12	0						12	5					

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined
Numerals represent the number of animals.
Vehicle: water for injection
*P<0.05, **P<0.01 : Significantly different from control (Mann-Whitney U test).
#P<0.05, ##P<0.01 : Significantly different from control (Fisher's exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 34-1(continued). Histopathological findings of female rats at the end of the dosing period

Group	Control (Vehicle)							SF 15 mg/kg							SF 50 mg/kg							SF 150/75 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver																												
Fatty change, hepatocyte, periportal	4	1	0	0	0		6	0	0	1	0	0		11	0	0	0	0	0		12	4	1	0	0	0		6
Hematopoiesis, extramedullary	4	1	0	0	0		6	1	0	0	0	0		11	0	0	0	0	0		12	5	0	0	0	0		6
Necrosis, focal	5	0	0	0	0		6	1	0	0	0	0		11	0	0	0	0	0		12	4	1	0	0	0		6
Nodule, hepatodiaphragmatic, focal hemorrhage	5					0	6	0					1	11	0					0	12	5					0	6
Pancreas	5						6	0						12	0						12	5						6
Stomach																												
Accumulation, lymphocyte, submucosa, glandular stomach	5	0	0	0	0		6	5	0	0	0	0		7	5	0	0	0	0		7	4	1	0	0	0		6
Cellular infiltration, eosinophil, lamina muscularis mucosa/submucosa, glandular stomach	2	3	0	0	0		6	0	4	1	0	0		7	0	1	3	1	0		7 *	0	1	2	2	0		6 *
Dendritic-like cell, increased, limiting ridge, mucosa	5	0	0	0	0		6	2	0	3	0	0		7	0	0	4	1	0		7 **, ##	2	0	1	2	0		6
Duodenum	5						6	0						12	0						12	5						6
Jejunum	5						6	0						12	0						12	5						6
Ileum	5						6	0						12	0						12	5						6
Cecum	5						6	0						12	0						12	5						6
Colon	5						6	0						12	0						12	5						6
Rectum	5						6	0						12	0						12	5						6
Lymph node, mesenteric	5						6	0						12	0						12	5						6
Spleen																												
Deposit, pigment, brown	0	0	0	4	1		6	0	0	0	0	0		12	0	0	0	0	0		12	0	0	0	5	0		6
Hematopoiesis, extramedullary	0	0	1	4	0		6	0	0	0	0	0		12	0	0	0	0	0		12	0	0	1	4	0		6

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined
Numerals represent the number of animals.
Vehicle: water for injection
*P<0.05, **P<0.01 : Significantly different from control (Mann-Whitney U test).
#P<0.05, ##P<0.01 : Significantly different from control (Fisher's exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 34-1(continued). Histopathological findings of female rats at the end of the dosing period

Group	Control (Vehicle)							SF 15 mg/kg							SF 50 mg/kg							SF 150/75 mg/kg							
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	
Kidney																													
Basophilic proximal tubule, straight	5	0	0	0	0		6	5	0	0	0	0		7	4	1	0	0	0		7	5	0	0	0	0		6	
Basophilic tubule, cortex	4	1	0	0	0		6	3	2	0	0	0		7	3	2	0	0	0		7	3	1	0	1	0		6	
Degeneration/necrosis, renal tubule, with mineralization	5	0	0	0	0		6	5	0	0	0	0		7	5	0	0	0	0		7	4	0	1	0	0		6	
Dilatation, lumen, distal tubule	5	0	0	0	0		6	5	0	0	0	0		7	5	0	0	0	0		7	4	1	0	0	0		6	
Mineralization, cortico-medullary junction/medulla	5	0	0	0	0		6	4	1	0	0	0		7	4	1	0	0	0		7	4	1	0	0	0		6	
Urinary bladder	5						6	0						12	0						12	5						6	
Adrenal gland	5						6	0						12	0						12	5						6	
Ovary	5						6	0						12	0						12	5						6	
Uterus	5						6	0						12	0						12	5						6	
Vagina	5						6	0						12	0						12	5						6	
Eyeball	5						6	0						12	0						12	5						6	
Harderian gland	5						6	0						12	0						12	5						6	
Sciatic nerve	5						6	0						12	0						12	5						6	
Skeletal muscle	5						6	0						12	0						12	5						6	
Femur																													
Deposit, basophilic substance, epiphysis/growth plate/metaphysis	5	0	0	0	0		6	5	0	0	0	0		7	5	0	0	0	0		7	0	1	0	4	0		6	**, ##
Marrow, femur																													
Hematopoiesis, increased	4	1	0	0	0		6	0	0	0	0	0		12	0	0	0	0	0		12	5	0	0	0	0		6	

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined
Numerals represent the number of animals.
Vehicle: water for injection
*P<0.05, **P<0.01 : Significantly different from control (Mann-Whitney U test).
#P<0.05, ##P<0.01 : Significantly different from control (Fisher's exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 34-2. Histopathological findings of female rats at the end of the dosing period, satellite group

Group	Control (Vehicle)							SF 150/75 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Brain	5							3						
Spinal cord	5							3						
Pituitary gland	5							3						
Submandibular gland	5							3						
Sublingual gland	5							3						
Lymph node, submandibular	5							3						
Thyroid gland														
Ectopic thymic tissue	5					0		2					1	
Ultimobranchial body	4					1		3					0	
Parathyroid gland	4						1	3						
Thymus														
Tingible body macrophage, increased	4	1	0	0	0			1	1	0	1	0		
Heart	5							3						
Trachea	5							3						
Lung														
Accumulation, foam cell, alveolus	5	0	0	0	0			2	1	0	0	0		
Bronchus	5							3						

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined
Numerals represent the number of animals.
Vehicle: water for injection
*P<0.05, **P<0.01 : Significantly different from control (Mann-Whitney U test).
#P<0.05, ##P<0.01 : Significantly different from control (Fisher's exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 34-2(continued). Histopathological findings of female rats at the end of the dosing period, satellite group

Group	Control (Vehicle)							SF 150/75 mg/kg							
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE	
Liver															
Fatty change, hepatocyte, periportal	5	0	0	0	0			2	1	0	0	0			
Microgranuloma	2	3	0	0	0			2	1	0	0	0			
Necrosis, focal	4	1	0	0	0			3	0	0	0	0			
Pancreas	5							3							
Stomach															
Cellular infiltration, eosinophil, lamina muscularis mucosa/submucosa, glandular stomach	0	3	2	0	0			0	0	1	2	0			
Dendritic-like cell, increased, limiting ridge, mucosa	4	1	0	0	0			0	0	2	1	0			**
Duodenum	5							3							
Jejunum	5							3							
Ileum	5							3							
Cecum	5							3							
Colon	5							3							
Rectum	5							3							
Lymph node, mesenteric	5							3							
Spleen															
Deposit, pigment, brown	0	0	0	5	0			0	0	0	3	0			
Hematopoiesis, extramedullary	0	5	0	0	0			0	3	0	0	0			

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined
Numerals represent the number of animals.
Vehicle: water for injection
*P<0.05, **P<0.01 : Significantly different from control (Mann-Whitney U test).
#P<0.05, ##P<0.01 : Significantly different from control (Fisher's exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 34-2(continued). Histopathological findings of female rats at the end of the dosing period, satellite group

Group	Control (Vehicle)							SF 150/75 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Kidney														
Basophilic tubule, cortex	4	1	0	0	0			1	2	0	0	0		
Urinary bladder	5							3						
Adrenal gland	5							3						
Ovary	5							3						
Uterus	5							3						
Vagina	5							3						
Eyeball	5							3						
Harderian gland	5							3						
Sciatic nerve	5							3						
Skeletal muscle	5							3						
Femur														
Deposit, basophilic substance, epiphysis/growth plate/metaphysis	5	0	0	0	0			0	0	3	0	0		**, #
Marrow, femur	5							3						

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined
Numerals represent the number of animals.
Vehicle: water for injection
*P<0.05, **P<0.01 : Significantly different from control (Mann-Whitney U test).
#P<0.05, ##P<0.01 : Significantly different from control (Fisher's exact test).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 34-3. Histopathological findings of female rats at the end of the recovery period

Findings	Group / Grade	Control (Vehicle) -	±	+	2+	3+	P	NE	SF 150/75 mg/kg -	±	+	2+	3+	P	NE
Brain		0						5	0						3
Spinal cord		0						5	0						3
Pituitary gland		0						5	0						3
Submandibular gland		0						5	0						3
Sublingual gland		0						5	0						3
Lymph node, submandibular		0						5	0						3
Thyroid gland		0						5	0						3
Parathyroid gland		0						5	0						3
Thymus		0						5	0						3
Heart															
Fibrosis, myocardial, diffuse		0	0	0	0	0		5	0	0	0	1	0		2
Degeneration/fibrosis, myocardial, focal		0	1	0	0	0		4	0	0	0	0	0		3
Trachea		0						5	0						3
Lung		0						5	0						3
Bronchus		0						5	0						3

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined
Numerals represent the number of animals.
Vehicle: water for injection
Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 34-3(continued). Histopathological findings of female rats at the end of the recovery period,

Group	Control (Vehicle)							SF 150/75 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Liver	0						5	0						3
Pancreas	0						5	0						3
Stomach														
Cellular infiltration, eosinophil, lamina muscularis mucosa/submucosa, glandular stomach	0	4	1	0	0			0	3	0	0	0		
Dendritic-like cell, increased, limiting ridge, mucosa	4	1	0	0	0			0	2	1	0	0		
Duodenum	0						5	0						3
Jejunum	0						5	0						3
Ileum	0						5	0						3
Cecum	0						5	0						3
Colon	0						5	0						3
Rectum	0						5	0						3
Lymph node, mesenteric	0						5	0						3
Spleen	0						5	0						3

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined
Numerals represent the number of animals.
Vehicle: water for injection
Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 34-3(continued). Histopathological findings of female rats at the end of the recovery period,

Group	Control (Vehicle)							SF 150/75 mg/kg						
Findings / Grade	-	±	+	2+	3+	P	NE	-	±	+	2+	3+	P	NE
Kidney														
Basophilic tubule, cortex	4	1	0	0	0			2	0	1	0	0		
Cyst, medulla	5					0		2					1	
Mineralization, cortico-medullary junction/medulla	5	0	0	0	0			1	1	1	0	0		
Urinary bladder	0						5	0						3
Adrenal gland	0						5	0						3
Ovary	0						5	0						3
Uterus	0						5	0						3
Vagina	0						5	0						3
Eyeball	0						5	0						3
Harderian gland	0						5	0						3
Sciatic nerve	0						5	0						3
Skeletal muscle	0						5	0						3
Femur	5							3						
Marrow, femur	0						5	0						3

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined
Numerals represent the number of animals.
Vehicle: water for injection
Not significantly different from control.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 35. Results of observations about estrous cycle

Dose	Control (vehicle: water for injection)	SF (15 mg/kg)	SF (50 mg/kg)	SF (150/75 mg/kg)
Number of animals examined	12	12	12	12
Pre-treatment period				
Number of animals showing type of cycle				
4-day cycle	11	10	10	8
4-5-day cycle	1	2	1	2
5-day cycle	0	0	1	2
Mean length of estrous cycle in days; Mean±S.D. (N)	4.0 ± 0.1 (12)	4.1 ± 0.2 (12)	4.1 ± 0.3 (12)	4.2 ± 0.4 (12)
Treatment period				
Number of animals showing each type of cycle				
4-day cycle	11	11	8	8
4-5-day cycle	0	1	1	2
5-day cycle	1	0	2	2
irreguler cycle	0	0	1	0
Mean length of estrous cycle in days; Mean±S.D. (N)	4.1 ± 0.3 (12)	4.0 ± 0.1 (12)	4.4 ± 0.6 (12)	4.3 ± 0.4 (12)
Frequency of animals that show abnormal estrous cycles after the treatment	0 / 12	0 / 12	1 / 12	0 / 12
Mean times of vaginal estrus during mating period; Mean±S.D. (N)	1.0 ± 0.0 (11)	1.0 ± 0.0 (12)	1.0 ± 0.0 (12)	1.0 ± 0.0 (12)

Significantly different from the control group (*: $p<0.05$, **: $p<0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 36. Results of observations about reproductive performance

Dose	Control (vehicle: water for injection)	SF (15 mg/kg)	SF (50 mg/kg)	SF (150/75 mg/kg)
Number of mated pairs [A]	12	12	12	12
Number of copulated pairs [B]	11	12	12	12
Copulation index [(B/A)×100,%]	91.7	100.0	100.0	100.0
Number of fertile males [C]	11	12	12	11#
Fertility index [(C/B)×100,%]	100.0	100.0	100.0	100.0
Pairing days until copulation ;Mean±S.D.(N)	2.6 ± 1.3 (11)	3.3 ± 3.6 (12)	2.3 ± 1.1 (12)	2.2 ± 0.7 (12)

#: One of paired females died on day 7 of pregnancy
Significantly different from the control group (*: $p<0.05$, **: $p<0.01$).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 37. Observation of offspring (F_1)

Group	Control (vehicle: water for injection)	SF 15 mg/kg	SF 50 mg/kg	SF 150/75 mg/kg
Number of dams	11	12	12	11
Gestation length (days)				
Mean ± S.D. per dam	21.9 ± 0.3	22.2 ± 0.4	22.0 ± 0.0	21.9 ± 0.5
Number of corpora lutea				
Total	165	194	182	179
Mean ± S.D. per dam	15.0 ± 1.0	16.2 ± 1.3	15.2 ± 1.3	16.3 ± 1.7
Number of implantation scars				
Total	163	191	174	177
Mean ± S.D. per dam	14.8 ± 0.9	15.9 ± 1.3	14.5 ± 0.9	16.1 ± 1.5 *
Implantation index (%) [a]	98.9 ± 2.5	98.5 ± 2.7	96.0 ± 6.4	99.0 ± 2.3
Delivery index (dams,%) [b]	100.0	100.0	100.0	100.0
Number of offspring at birth				
Total	161	177	168	169
Mean ± S.D. per dam	14.6 ± 1.1	14.8 ± 1.8	14.0 ± 1.0	15.4 ± 1.6
Number of live offspring at birth				
Male	79	78	78	74
Female	81	97	89	93
Total	160	175	167	167
Mean ± S.D. per dam	14.5 ± 1.4	14.6 ± 1.5	13.9 ± 1.0	15.2 ± 1.7
Sex ratio [c]				
Mean ± S.D. per dam	0.49 ± 0.13	0.45 ± 0.15	0.47 ± 0.13	0.44 ± 0.14
Number of dead offspring				
Total	1	2	1	2
Mean ± S.D. per dam	0.1 ± 0.3	0.2 ± 0.4	0.1 ± 0.3	0.2 ± 0.4
Delivery index (offspring) [d]				
Mean% ± S.D. per dam	98.7 ± 2.9	92.7 ± 7.6	96.6 ± 4.6	95.5 ± 4.2
Birth index [e]				
Mean% ± S.D. per dam	98.0 ± 4.9	91.7 ± 7.3	96.1 ± 5.2	94.4 ± 6.1
Live birth index [f]				
Mean% ± S.D. per dam	99.2 ± 2.5	99.0 ± 2.2	99.4 ± 1.9	98.8 ± 2.8
Number of offspring on day 4				
Male	76	77	77	72
Female	80	97	88	92
Sex ratio [c]				
Mean ± S.D. per dam	0.48 ± 0.14	0.45 ± 0.15	0.47 ± 0.14	0.44 ± 0.14
Viability index [g]				
Mean% ± S.D. per dam	97.5 ± 3.4	99.5 ± 1.8	98.9 ± 2.7	98.1 ± 6.5
Number of external abnormalities [i]	0	0	0	0
Mean% ± S.D. per dam	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

Significantly different from the control group (*: P<0.05, **: P<0.01).
a): (Number of implantation scars/Number of corpora lutea)×100.
b): (Number of dams with live offspring/number of pregnant dams)×100.
c): Number of male offspring/(number of male offspring + number of female offspring).
d): (Number of offspring at birth/Number of implantation scars)×100.
e): (Number of live offspring at birth/number of implantation scars)×100.
f): (Number of live offspring at birth/number of offspring at birth)×100.
g): (Number of live offspring 4 days after birth/number of live offspring at birth)×100.
h): (Number of live offspring 21 days after birth/number of live offspring after culling)×100.
i): Number of external abnormalities in live offspring at birth.
Figures in parentheses indicate number of dams.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 38. Body weights of offspring (F_1) before weaning

Group		Control (vehicle: water for injection)	SF 15 mg/kg	SF 50 mg/kg	SF 150/75 mg/kg
Number of dams		11	12	12	11
Male					
Days after birth					
	0	6.7 ± 0.2	6.9 ± 0.8	7.0 ± 0.3	6.4 ± 0.3
	4	10.5 ± 0.6	11.1 ± 1.3	11.3 ± 0.7	9.8 ± 1.4
Number of dams		11	12	12	11
Female					
Days after birth					
	0	6.3 ± 0.4	6.4 ± 0.6	6.7 ± 0.2	6.0 ± 0.3
	4	9.9 ± 0.6	10.2 ± 1.0	10.9 ± 0.7 *	9.2 ± 1.3

Each value shows mean ± S.D. per dam. (g).
Figures in parentheses indicate number of dams.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 39. General conditions in offspring (F_1) before weaning

Group	mg/kg	Number of offspring and general conditions	Days after birth 0	1	2	3	4
Control (vehicle: water for injection)		Number of offspring	160	160	159	157	157
		General appearance, No abnormality	160	159	157	157	156
		General appearance, Death		1	2		1
SF 15 mg/kg		Number of offspring	175	175	174	174	174
		General appearance, No abnormality	175	174	174	174	174
		General appearance, Death		1			
SF 50 mg/kg		Number of offspring	167	167	165	165	165
		General appearance, No abnormality	167	164	165	165	165
		General appearance, Death		3			
SF 150/75 mg/kg		Number of offspring	167	167	167	166	165
		General appearance, No abnormality	167	167	166	165	164
		General appearance, Death			1	1	1
		Number of offspring					

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Table 40. Morphological observations of offspring (F_1)

Group	Control (vehicle: wter for injection)	SF 15 mg/kg	SF 50 mg/kg	SF 150/75 mg/kg
Dead pups				
Number of dead pups [a)]	4	3	3	5
Number of missing pups	1	1	2	1
Number of dead pups examined	3	2	1	4
Number of dead pups with external changes	0	1	0	0
Anasarca and anal atresia		1		
Number of dead pups with visceral changes	0	0	0	0
Live pups				
Number of live pups examined (postnatal day 0)	160	175	167	167
Number of live pups with external changes	0	0	0	0
Number of live pups examined (postnatal day 4)	157	174	165	164
Number of live pups with external changes	0	0	0	0
Number of live pups with visceral changes	0	0	0	0

[a)] including missing pups

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 1-1-1. General conditions of male rats

Control (vehicle: water for injection)

Male No.	Days of administration																																																	
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M01001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
d	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
a: Behavior, Decrease in locomotor activity.
b: General appearance, Emaciation.
c: Skin, Crust formation.
d: General appearance, Death.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 1-1-1(continued). General conditions of male rats

Control (vehicle: water for injection)

Male No.	Days of administration																																				
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
M01001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	7
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Skin, Crust formation.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 1-1-2. General conditions of male rats

SF 15 mg/kg

Male No.	Days of administration																																																	
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	c	c	c	c
M02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	11	11
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1
d	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
a: Behavior, Decrease in locomotor activity.
b: General appearance, Emaciation.
c: Skin, Crust formation.
d: General appearance, Death.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 1-1-2(continued). General conditions of male rats

SF 15 mg/kg

Male No.	Days of administration																																				
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
M02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02018	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a	a	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M02024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
-	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
a	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Skin, Crust formation.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 1-1-3. General conditions of male rats

SF 50 mg/kg

Male No.	Days of administration																																																	
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
d	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
a: Behavior, Decrease in locomotor activity.
b: General appearance, Emaciation.
c: Skin, Crust formation.
d: General appearance, Death.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 1-1-3(continued). General conditions of male rats

SF 50 mg/kg

Male No.	Days of administration																																				
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	
M03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M03036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Skin, Crust formation.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 1-1-4. General conditions of male rats

SF 150/75 mg/kg

Male No.	Days of administration																																																	
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
M04037	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04038	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a,b,d																					
M04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
d	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Behavior, Decrease in locomotor activity.

b: General appearance, Emaciation.

c: Skin, Crust formation.

d: General appearance, Death.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 1-1-4(continued). General conditions of male rats

SF 150/75 mg/kg

Male No.	Days of administration																																				
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
M04037	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04038	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
M04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of males	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	6
-	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	6
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Skin, Crust formation.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 1-2-1. General conditions of male rats at the recovery period

Control (vehicle: water for injection)

Male No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
M01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
-	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

-: General appearance, No abnormality.
a: Mouth, Loss of teeth.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 1-2-2. General conditions of male rats at the recovery period

SF 150/75 mg/kg

Male No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
M04043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
M04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a
M04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
-	5	5	5	5	5	5	5	5	5	5	5	5	5	5	4
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1

-: General appearance, No abnormality.
a: Mouth, Loss of teeth.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 2-1-1. General conditions of female rats

Control (vehicle: water for injection)

Female No.	Days of administration																																																	
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F01001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-														
F01002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																
F01003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																		
F01004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																		
F01005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																				
F01006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																				
F01007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-														
F01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-														
F01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																
F01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																				
F01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-														
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	9	9	7	7	5	5	1	1	1	1	1	1	1	1	1	1	1	1	1	1
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	9	9	7	7	5	5	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 2-1-1 (continued). General conditions of female rats

Control (vehicle: water for injection)

Female No.	Days of administration																																																	
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43		44		45		46		47		48		49		50	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F01011	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
-	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 2-1-1 (continued). General conditions of female rats

Control (vehicle: water for injection)

Female No.	Days of administration				
	51		52		53
	Pre	Post	Pre	Post	Pre
F01011	-	-	-	-	-
Number of females	1	1	1	1	1
-	1	1	1	1	1

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 2-1-2. General conditions of female rats

SF 15 mg/kg

Female No.	Days of administration																																																	
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																						
F02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																						
F02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																				
F02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																						
F02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																						
F02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																				
F02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-														
F02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-														
F02021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																
F02023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																
F02024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-														
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	6	6	4	4	1	1	1	1	1	1	1	1	1	1	1	1	1	1
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	8	8	6	6	4	4	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 2-1-2(continued) . General conditions of female rats

SF 15 mg/kg

Female No.	Days of administration																																																	
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43		44		45		46		47		48		49		50	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F02021	-	-	-	-	-	-																																												
Number of females	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 2-1-3. General conditions of female rats

SF 50 mg/kg

Female No.	Days of administration																																																	
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																		
F03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																		
F03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-														
F03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																
F03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																
F03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																				
F03031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																		
F03032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-														
F03033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																				
F03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																
F03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																		
F03036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																				
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	9	9	5	5	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	9	9	5	5	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 2-1-4. General conditions of female rats

SF 150/75 mg/kg

Female No.	Days of administration																																																	
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F04037	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																				
F04038	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																				
F04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																		
F04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																				
F04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																				
F04042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																				
F04043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																				
F04044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																				
F04045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																				
F04046	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																
F04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																				
F04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-																
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	3	3	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	3	3	2	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 2-2-1. General conditions of female rats, satellite group

Control (vehicle: water for injection)

Female No.	Days of administration																																																	
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F05049	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05050	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05051	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05052	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05053	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05054	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05055	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05056	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05057	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05058	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
-	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
d	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
e	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
f	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
g	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
h	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
i	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
j	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
k	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
l	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
m	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
n	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
a: Skin, Reddening of the auricle.
b: Fur, Hair, Coat, Piloerection.
c: Eye, Eyeball, Bulbi, Globe, Incomplete eyelid opening.
d: General appearance, Emaciation.
e: Eye, Eyeball, Bulbi, Globe, Reddish tear.
f: Excretion, Decrease in amount of feces.
g: General appearance, Death.
h: Posture, Body position, Prone position.
i: Nose, Smudge of perinasal area.
j: Fur, Hair, Coat, Soiled fur.
k: Skin, Cyanosis.
l: Posture, Body position, Crouching position.
m: Nervous system, Convulsion.
n: Body temperature, Hypothermia.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 2-2-1(continued). General conditions of female rats, satellite group

Control (vehicle: water for injection)

Female No.	Days of administration																																			
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F05049	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05050	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05051	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05052	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05053	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05054	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05055	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05056	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05057	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F05058	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5
-	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	5
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
d	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
e	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
f	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
a: Eye, Eyeball, Bulbi, Globe, Reddish tear.
b: Eye, Eyeball, Bulbi, Globe, Incomplete eyelid opening.
c: Fur, Hair, Coat, Soiled fur.
d: Fur, Hair, Coat, Piloerection.
e: General appearance, Death.
f: Posture, Body position, Prone position.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 2-2-2. General conditions of female rats, satellite group

SF 150/75 mg/kg

Female No.	Days of administration																																																	
	1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22		23		24		25	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F06059	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06060	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a,i	a	a,b,d,f	a,b,d,f,n	g	
F06061	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a,d,h	a,d,h	a,d,h	g							
F06062	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06063	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	b,c,d,k,m	g									
F06064	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06065	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	b	-	-
F06066	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	b,c,l	c,i	c,i	a,f	a,f	-	-
F06067	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06068	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	9	9	8	8	8	8	8	8	7
-	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	8	8	8	8	7	6	6	6	5	7	7
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	1	1	2	2	0	0
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	1	2	0	0
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	1	1	0	0	0	0
d	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	1	1	0	0	0	0	1	1	0	0
e	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
f	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	2	0	0
g	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	1	0
h	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0	0	0	0
i	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	1	0	0	0	0
j	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
k	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
l	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0
m	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
n	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0

Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
a: Skin, Reddening of the auricle.
b: Fur, Hair, Coat, Piloerection.
c: Eye, Eyeball, Bulbi, Globe, Incomplete eyelid opening.
d: General appearance, Emaciation.
e: Eye, Eyeball, Bulbi, Globe, Reddish tear.
f: Excretion, Decrease in amount of feces.
g: General appearance, Death.
h: Posture, Body position, Prone position.
i: Nose, Smudge of perinasal area.
j: Fur, Hair, Coat, Soiled fur.
k: Skin, Cyanosis.
l: Posture, Body position, Crouching position.
m: Nervous system, Convulsion.
n: Body temperature, Hypothermia.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 2-2-2(continued). General conditions of female rats, satellite group

SF 150/75 mg/kg

Female No.	Days of administration																																			
	26		27		28		29		30		31		32		33		34		35		36		37		38		39		40		41		42		43
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F06059	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06062	-	-	b,c,d	b,c,d,f	e																														
F06064	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06065	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06066	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F06067	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	a	a	a	a	a	a	
F06068	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Number of females	7	7	7	7	7	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	3
-	7	7	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	5	5	5	5	5	5	3
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1	1	1	0
b	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
c	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
d	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
e	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
f	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
a: Eye, Eyeball, Bulbi, Globe, Reddish tear.
b: Eye, Eyeball, Bulbi, Globe, Incomplete eyelid opening.
c: Fur, Hair, Coat, Soiled fur.
d: Fur, Hair, Coat, Piloerection.
e: General appearance, Death.
f: Posture, Body position, Prone position.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 2-3-1. General conditions of female rats at the recovery period

Control (vehicle: water for injection)

Female No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
F05054	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05055	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05056	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05057	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F05058	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
-	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

-: General appearance, No abnormality.
a: Eye, Eyeball, Bulbi, Globe, Reddish tear.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 2-3-2. General conditions of female rats at the recovery period

SF 150/75 mg/kg

Female No.	Days of recovery														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
F06066	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F06067	a	a	a	-	a	a	a	a	-	a	a	-	-	-	-
F06068	-	-	-	-	-	-	-	-	-	-	-	-	-	a	-
Number of females	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
-	2	2	2	3	2	2	2	2	3	2	2	3	3	2	3
a	1	1	1	0	1	1	1	1	0	1	1	0	0	1	0

-: General appearance, No abnormality.
a: Eye, Eyeball, Bulbi, Globe, Reddish tear.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 3-1. General conditions in dams during pregnancy

Control (vehicle: water for injection)

Dam No.	Days of pregnancy																																															
	0		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F01001	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
F01002	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01003	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
F01004	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
F01005	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
F01006	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
F01007	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01008	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
F01009	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F01010	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-				
F01012	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	4	4
-	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	4	4
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
d	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
e	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
f	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
g	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

>: Excluded from analysis (not pregnant)
Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
a: Fur, Hair, Coat, Piloerection.
b: Excretion, Decrease in amount of feces.
c: Mouth, Perioral smudge.
d: Eye, Eyeball, Bulbi, Globe, Incomplete eyelid opening.
e: Posture, Body position, Crouching position.
f: General appearance, Emaciation.
g: General appearance, Death.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 3-2. General conditions in dams during pregnancy

SF 15 mg/kg

Dam No.	Days of pregnancy																																													
	0		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F02013	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02014	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02015	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02016	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
F02017	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02018	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02019	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02020	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02021	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02022	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F02023	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F02024	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5	4
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5	4
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
d	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
e	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
f	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
g	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

>: Excluded from analysis (not pregnant)
Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
a: Fur, Hair, Coat, Piloerection.
b: Excretion, Decrease in amount of feces.
c: Mouth, Perioral smudge.
d: Eye, Eyeball, Bulbi, Globe, Incomplete eyelid opening.
e: Posture, Body position, Crouching position.
f: General appearance, Emaciation.
g: General appearance, Death.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 3-3. General conditions in dams during pregnancy

SF 50 mg/kg

Dam No.	Days of pregnancy																																													
	0		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F03025	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03026	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03027	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03028	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03029	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03030	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03031	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03032	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03033	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03034	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F03035	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
F03036	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-		
Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5	5
-	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	5	5
a	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
b	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
c	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
d	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
e	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
f	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
g	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

>: Excluded from analysis (not pregnant)
Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
a: Fur, Hair, Coat, Piloerection.
b: Excretion, Decrease in amount of feces.
c: Mouth, Perioral smudge.
d: Eye, Eyeball, Bulbi, Globe, Incomplete cyclid opening.
e: Posture, Body position, Crouching position.
f: General appearance, Emaciation.
g: General appearance, Death.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 3-4. General conditions in dams during pregnancy

SF 150/75 mg/kg

Dam No.	Days of pregnancy																																																	
	0		1		2		3		4		5		6		7		8		9		10		11		12		13		14		15		16		17		18		19		20		21		22	
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
F04037	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04038	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04039	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04040	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04041	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04042	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04043	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04044	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04045	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04046	-	-	-	-	-	-	-	-	a,d	a	a,b,c	a,b,c,e	a,b,c,f	a,b,c,d,e,f	g																																			
F04047	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
F04048	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Number of dams	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	3	3
-	12	12	12	12	12	12	12	12	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	3	3
a	0	0	0	0	0	0	0	0	1	1	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
b	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
c	0	0	0	0	0	0	0	0	0	0	1	1	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
d	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
e	0	0	0	0	0	0	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
f	0	0	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
g	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

>: Excluded from analysis (not pregnant)
Pre: Before administration, Post: after administration.
-: General appearance, No abnormality.
a: Fur, Hair, Coat, Piloerection.
b: Excretion, Decrease in amount of feces.
c: Mouth, Perioral smudge.
d: Eye, Eyeball, Bulbi, Globe, Incomplete eyelid opening.
e: Posture, Body position, Crouching position.
f: General appearance, Emaciation.
g: General appearance, Death.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 4-1. General conditions in dams during lactation

Control (vehicle: water for injection)

Dam No.	Days of lactation										
	0		1		2		3		4		5
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F01001	#	#	-	-	-	-	-	-	-	-	-
F01002	#	#	-	-	-	-	-	-	-	-	-
F01003	-	-	-	-	-	-	-	-	-	-	-
F01004	-	-	-	-	-	-	-	-	-	-	-
F01005	-	-	-	-	-	-	-	-	-	-	-
F01006	-	-	-	-	-	-	-	-	-	-	-
F01007	#	#	-	-	-	-	-	-	-	-	-
F01008	-	-	-	-	-	-	-	-	-	-	-
F01009	#	#	-	-	-	-	-	-	-	-	-
F01010	-	-	-	-	-	-	-	-	-	-	-
F01012	#	#	-	-	-	-	-	-	-	-	-
Number of dams	6	6	11	11	11	11	11	11	11	11	11
-	6	6	11	11	11	11	11	11	11	11	11
a	0	0	0	0	0	0	0	0	0	0	0

#, Animal was administered to dosing formulation before delivery, and no abnormality was observed on day 0 of lactation.

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Behavior, Decrease in locomotor activity.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 4-2. General conditions in dams during lactation

SF 15 mg/kg

Dam No.	Days of lactation										
	0		1		2		3		4		5
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F02013	-	-	-	-	-	-	-	-	-	-	-
F02014	-	-	-	-	-	-	-	-	-	-	-
F02015	-	-	-	-	-	-	-	-	-	-	-
F02016	#	#	-	-	-	-	-	-	-	-	-
F02017	-	-	-	-	-	-	-	-	-	-	-
F02018	-	-	-	-	-	-	-	-	-	-	-
F02019	#	#	-	-	-	-	-	-	-	-	-
F02020	-	-	-	-	-	-	-	-	-	-	-
F02021	-	-	-	-	-	-	-	-	-	-	-
F02022	-	-	-	-	-	-	-	-	-	-	-
F02023	#	#	-	-	-	-	-	-	-	-	-
F02024	-	-	-	-	-	-	-	-	-	-	-
Number of dams	9	10	12	12	12	12	12	12	12	12	12
-	9	10	12	12	12	12	12	12	12	12	12
a	0	0	0	0	0	0	0	0	0	0	0

#, Animal was administered to dosing formulation before delivery, and no abnormality was observed on day 0 of lactation.

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Behavior, Decrease in locomotor activity.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 4-3. General conditions in dams during lactation

SF 50 mg/kg

Dam No.	Days of lactation										
	0		1		2		3		4		5
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F03025	#	#	-	-	-	-	-	-	-	-	-
F03026	#	#	-	-	-	-	-	-	-	-	-
F03027	#	#	-	-	-	-	-	-	-	-	-
F03028	-	-	-	-	-	-	-	-	-	-	-
F03029	-	-	-	-	-	-	-	-	-	-	-
F03030	-	-	-	-	-	-	-	-	-	-	-
F03031	-	-	-	-	-	-	-	-	-	-	-
F03032	#	#	-	-	-	-	-	-	-	-	-
F03033	-	-	-	-	-	-	-	-	-	-	-
F03034	#	#	-	-	-	-	-	-	-	-	-
F03035	-	-	-	-	-	-	-	-	-	-	-
F03036	-	-	-	-	-	-	-	-	-	-	-
Number of dams	7	7	12	12	12	12	12	12	12	12	12
-	7	7	12	12	12	12	12	12	12	12	12
a	0	0	0	0	0	0	0	0	0	0	0

#, Animal was administered to dosing formulation before delivery, and no abnormality was observed on day 0 of lactation.

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Behavior, Decrease in locomotor activity.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 4-4. General conditions in dams during lactation

SF 150/75 mg/kg

Dam No.	Days of lactation										
	0		1		2		3		4		5
	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre
F04037	-	-	-	-	-	-	-	-	-	-	-
F04038	#	#	-	-	-	-	-	-	-	-	-
F04039	-	-	-	-	-	-	-	-	-	-	-
F04040	-	-	a	a	-	-	-	-	-	-	-
F04041	-	-	-	-	-	-	-	-	-	-	-
F04042	-	-	-	-	-	-	-	-	-	-	-
F04043	-	-	-	-	-	-	-	-	-	-	-
F04044	#	#	-	-	-	-	-	-	-	-	-
F04045	#	#	-	-	-	-	-	-	-	-	-
F04047	#	#	-	-	-	-	-	-	-	-	-
F04048	-	-	-	-	-	-	-	-	-	-	-
Number of dams	7	7	11	11	11	11	11	11	11	11	11
-	7	7	10	10	11	11	11	11	11	11	11
a	0	0	1	1	0	0	0	0	0	0	0

#, Animal was administered to dosing formulation before delivery, and no abnormality was observed on day 0 of lactation.

Pre: Before administration, Post: after administration.

-: General appearance, No abnormality.

a: Behavior, Decrease in locomotor activity.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 5-1. Detailed clinical observations of male rats

Control (vehicle: water for injection)

Male No.	Observations made while handling																		Open-field observations																				
	Behavior while removing from cage									Lacrimation									Vocalization									Touch response								
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	R7 [c]	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
M01001	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M01002	2	2	3	2	2	3	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	3	2		
M01003	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M01004	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M01005	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M01006	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M01007	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M01008	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M01009	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M01010	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M01011	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M01012	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total	3:0	3:0	3:1	3:0	3:0	3:1	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:1	3:0	3:0	3:0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)

[a] pre-treatment; [b] day 8 of treatment; [c] day 7 of recovery
Behavior while removing from cage [2, normal; 3, hard]
Lacrimation [2, not observed; 3, slight]
Vocalization [2, unheard; 3, heard]
Touch response [2, normal; 3, sensitive]

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 5-1(continued). Detailed clinical observations of male rats

Control (vehicle: water for injection)

Male No.	Open-field observations																	
	Urination									Defecation								
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	R7 [c]	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
M01001	0	0	0	0	0	0	0			0	1	0	0	0	0	0		
M01002	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M01003	0	0	0	0	0	1	0			0	0	0	0	0	0	0		
M01004	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M01005	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M01006	0	0	1	0	0	0	0			0	0	0	0	0	0	0		
M01007	3	1	2	1	0	0	0			1	0	0	0	2	0	0		
M01008	0	0	1	0	1	1	1	2	1	0	0	0	0	0	0	0	0	0
M01009	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M01010	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M01011	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M01012	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	3	1	4	1	1	2	1	2	1	1	1	0	0	2	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(5)	(5)

[a] pre-treatment; [b] day 8 of treatment; [c] day 7 of recovery
Urination [frequency/30sec]
Defecation [frequency/30sec]

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 5-2. Detailed clinical observations of male rats

SF 15 mg/kg

Male No.	Observations made while handling																		Open-field observations																				
	Behavior while removing from cage									Lacrimation									Vocalization									Touch response										
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	R7 [c]	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
M02013	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M02014	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M02015	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M02016	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M02017	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M02018	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M02019	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M02020	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M02021	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M02022	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M02023	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M02024	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
Total score	3:0	3:0	3:0	3:0	3:0	3:0	3:0			3:0	3:0	3:0	3:0	3:0	3:0	3:0			3:0	3:0	3:0	3:0	3:0	3:0	3:0			3:0	3:0	3:0	3:0	3:0	3:0	3:0		
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)			(12)	(12)	(12)	(12)	(12)	(12)	(12)			(12)	(12)	(12)	(12)	(12)	(12)	(12)			(12)	(12)	(12)	(12)	(12)	(12)	(12)		

[a] pre-treatment; [b] day 8 of treatment; [c] day 7 of recovery
Behavior while removing from cage [2, normal; 3, hard]
Lacrimation [2, not observed; 3, slight]
Vocalization [2, unheard; 3, heard]
Touch response [2, normal; 3, sensitive]

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 5-2(continued). Detailed clinical observations of male rats

SF 15 mg/kg

Male No.	Open-field observations													
	Urination							Defecation						
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42
M02013	0	0	0	0	1	1	1	0	0	1	0	0	0	0
M02014	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02015	0	0	0	1	0	0	0	0	0	0	0	0	0	0
M02016	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02017	1	0	0	0	0	1	1	0	0	0	0	0	0	0
M02018	0	1	2	0	0	0	0	0	1	3	0	0	0	0
M02019	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02020	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02021	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02022	0	2	2	0	0	0	0	0	1	0	0	0	0	0
M02023	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M02024	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total score	1	3	4	1	1	2	2	0	2	4	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

[a] pre-treatment; [b] day 8 of treatment

Urination [frequency/30sec]

Defecation [frequency/30sec]

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 5-3. Detailed clinical observations of male rats

SF 50 mg/kg

Male No.	Observations made while handling																			Open-field observations																				
	Behavior while removing from cage									Lacrimation										Vocalization									Touch response										
	Pre[a]	T8[b]	T15	T24	T30	T36	T42	R7[c]	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
M03025	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	3	2	2	2	2			2	2	2	2	2	2	2		
M03026	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M03027	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M03028	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	3	2	2	2	2			2	2	3	2	2	2	2		
M03029	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M03030	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M03031	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M03032	2	2	3	2	2	2	2			2	2	2	2	2	2	2			2	2	3	2	2	2	2			2	2	2	2	2	2	2		
M03033	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M03034	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M03035	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M03036	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	3	2	2	2	2			2	2	2	2	2	2	2		
Total score	3: 0	3: 0	3: 1	3: 0	3: 0	3: 0	3: 0			3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0			3: 0	3: 0	3: 4	3: 0	3: 0	3: 0	3: 0			3: 0	3: 0	3: 1	3: 0	3: 0	3: 0	3: 0		
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)			(12)	(12)	(12)	(12)	(12)	(12)	(12)			(12)	(12)	(12)	(12)	(12)	(12)	(12)			(12)	(12)	(12)	(12)	(12)	(12)	(12)		

[a] pre-treatment; [b] day 8 of treatment; [c] day 7 of recovery

Behavior while removing from cage [2, normal; 3, hard]

Lacrimation [2, not observed; 3, slight]

Vocalization [2, unheard; 3, heard]

Touch response [2, normal; 3, sensitive]

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 5-3(continued). Detailed clinical observations of male rats

SF 50 mg/kg

Male No.	Open-field observations													
	Urination							Defecation						
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	Pre	T8	T15	T24	T30	T36	T42
M03025	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03026	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03027	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03028	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03029	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03030	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03031	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03032	0	0	3	0	0	1	0	0	0	1	0	0	1	0
M03033	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M03034	1	0	0	0	0	0	0	0	0	0	0	0	0	0
M03035	0	0	0	0	0	1	1	0	0	0	0	0	0	0
M03036	1	0	0	0	0	0	0	1	0	0	0	0	0	0
Total score	2	0	3	0	0	2	1	1	0	1	0	0	1	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(12)

[a] pre-treatment; [b] day 8 of treatment

Urination [frequency/30sec]

Defecation [frequency/30sec]

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 5-4. Detailed clinical observations of male rats

SF 150/75 mg/kg

Male No.	Observations made while handling																			Open-field observations																				
	Behavior while removing from cage									Lacrimation									Vocalization									Touch response								
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	R7 [c]	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
M04037	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04038	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04039	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04040	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04041	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04042	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
M04043	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04044	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	2	2	2
M04045	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04046	2	2	Died on day 15 of treatment							2	2	Died on day 15 of treatment							2	2	Died on day 15 of treatment							2	2	Died on day 15 of treatment						
M04047	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
M04048	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total score	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:1	3:0	3:0	3:0
(N)	(12)	(12)	(11)	(11)	(11)	(11)	(11)	(5)	(5)	(12)	(12)	(11)	(11)	(11)	(11)	(11)	(5)	(5)	(12)	(12)	(11)	(11)	(11)	(11)	(11)	(5)	(5)	(12)	(12)	(11)	(11)	(11)	(11)	(11)	(5)	(5)

[a] pre-treatment; [b] day 8 of treatment; [c] day 7 of recovery
Behavior while removing from cage [2, normal; 3, hard]
Lacrimation [2, not observed; 3, slight]
Vocalization [2, unheard; 3, heard]
Touch response [2, normal; 3, sensitive]

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 5-4(continued). Detailed clinical observations of male rats

SF 150/75 mg/kg

Male No.	Open-field observations																	
	Urination									Defecation								
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	R7 [c]	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
M04037	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M04038	2	0	1	0	1	0	0			3	0	0	0	0	0	0		
M04039	0	0	0	0	0	1	1			0	0	0	0	0	0	0		
M04040	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
M04041	0	0	0	0	0	0	1			0	0	0	0	0	0	0		
M04042	0	0	1	0	0	0	0			0	0	0	0	0	0	0		
M04043	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M04044	2	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
M04045	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
M04046	0	0	Died on day 15 of treatment							0	0	Died on day 15 of treatment						
M04047	0	0	0	0	0	1	0	1	1	0	0	0	0	0	0	0	0	0
M04048	2	0	0	0	0	1	0	0	0	1	0	0	0	0	0	0	0	0
Total score	7	0	3	0	1	4	2	1	1	4	0	0	0	0	0	0	0	0
(N)	(12)	(12)	(11)	(11)	(11)	(11)	(11)	(5)	(5)	(12)	(12)	(11)	(11)	(11)	(11)	(11)	(5)	(5)

[a] pre-treatment; [b] day 8 of treatment; [c] day 7 of recovery
Urination [frequency/30sec]
Defecation [frequency/30sec]

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 6-1-1. Detailed clinical observations of female rats

Control (vehicle: water for injection)

Female No.	Observations made while handling																				Open-field observations																			
	Behavior while removing from cage									Lacrimation									Vocalization									Touch response								
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	T49	L [c]	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	T49	L [c]	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	T49	L [c]	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	T49	L [c]
F01001	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F01002	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F01003	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F01004	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F01005	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F01006	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F01007	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F01008	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F01009	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F01010	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F01011	2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2	
F01012	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
Total score	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(1)	(11)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(1)	(11)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(1)	(11)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(1)	(11)

[a] pre-treatment; [b] day 8 of treatment; [c] day 7 of recovery
Behavior while removing from cage [2, normal; 3, hard]
Lacrimation [2, not observed; 3, slight]
Vocalization [2, unheard; 3, heard]
Touch response [2, normal; 3, sensitive]

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 6-1-1(continued). Detailed clinical observations of female rats

Control (vehicle: water for injection)

Female No.	Open-field observations																	
	Urination									Defecation								
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	T49	L [c]	Pre	T8	T15	T24	T30	T36	T42	T49	L
F01001	1	1	1	2	1	0			1	1	0	0	1	0	1			1
F01002	0	0	0	0	0	0			1	0	0	0	0	0	0			0
F01003	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F01004	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F01005	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F01006	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F01007	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F01008	1	0	0	0	0	0			0	0	0	0	0	0	0			0
F01009	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F01010	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F01011	0	0	0	0	0	0	0	0		0	0	0	0	0	0	0	0	
F01012	0	0	0	0	0	0			0	0	0	0	0	0	0			0
Total score	2	1	1	2	1	0	0	0	2	1	0	0	1	0	1	0	0	1
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(1)	(11)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(1)	(11)

[a] pre-treatment; [b] day 8 of treatment; [c] lactation period

Urination [frequency/30sec]
Defecation [frequency/30sec]

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 6-1-2. Detailed clinical observations of female rats

SF 15 mg/kg

Female No.	Observations made while handling																		Open-field observations																	
	Behavior while removing from cage									Lacrimation									Vocalization									Touch response								
	Pre[a]	T8[b]	T15	T24	T30	T36	T42	T49	L[c]	Pre[a]	T8[b]	T15	T24	T30	T36	T42	T49	L[c]	Pre[a]	T8[b]	T15	T24	T30	T36	T42	T49	L[c]	Pre[a]	T8[b]	T15	T24	T30	T36	T42	T49	L[c]
F02013	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F02014	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F02015	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F02016	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F02017	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F02018	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F02019	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F02020	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F02021	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2		2	2	2	2	2	2	2	2		2
F02022	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F02023	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F02024	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
Total score	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(0)	(12)

[a] pre-treatment; [b] day 8 of treatment; [c] day 7 of recovery

Behavior while removing from cage [2, normal; 3, hard]

Lacrimation [2, not observed; 3, slight]

Vocalization [2, unheard; 3, heard]

Touch response [2, normal; 3, sensitive]

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 6-1-2(continued). Detailed clinical observations of female rats

SF 15 mg/kg

Female No.	Open-field observations																	
	Urination									Defecation								
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	T49	L [c]	Pre	T8	T15	T24	T30	T36	T42	T49	L
F02013	0	0	1	0	1	0			0	0	0	0	0	0	0			0
F02014	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F02015	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F02016	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F02017	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F02018	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F02019	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F02020	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F02021	0	2	0	1	1	0	1		0	0	0	0	0	0	0	0		0
F02022	0	0	0	0	0	1			0	0	0	0	0	0	0			0
F02023	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F02024	0	0	0	0	0	0			0	0	0	0	0	0	0			0
Total score	0	2	1	1	2	1	1	0	0	0	0	0	0	0	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(1)	(0)	(12)

[a] pre-treatment; [b] day 8 of treatment; [c] lactation period

Urination [frequency/30sec]
Defecation [frequency/30sec]

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 6-1-3. Detailed clinical observations of female rats

SF 50 mg/kg

Female No.	Observations made while handling																				Open-field observations																					
	Behavior while removing from cage									Lacrimation									Vocalization									Touch response								
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	T49	L [c]	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	T49	L [c]	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	T49	L [c]	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	T49	L [c]
F03025	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F03026	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F03027	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F03028	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F03029	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F03030	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F03031	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F03032	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F03033	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F03034	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F03035	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F03036	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
Total score	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0	3:0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(0)	(12)

[a] pre-treatment; [b] day 8 of treatment; [c] day 7 of recovery
Behavior while removing from cage [2, normal; 3, hard]
Lacrimation [2, not observed; 3, slight]
Vocalization [2, unheard; 3, heard]
Touch response [2, normal; 3, sensitive]

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 6-1-3(continued). Detailed clinical observations of female rats

SF 50 mg/kg

Female No.	Open-field observations																	
	Urination									Defecation								
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	T49	L [c]	Pre	T8	T15	T24	T30	T36	T42	T49	L
F03025	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F03026	0	0	0	0	0	0			1	0	0	0	0	0	0			0
F03027	0	0	0	0	0	0			1	0	0	0	0	0	0			0
F03028	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F03029	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F03030	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F03031	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F03032	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F03033	0	0	0	0	0	1			0	0	0	0	0	0	0			0
F03034	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F03035	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F03036	0	0	0	0	0	0			0	0	0	0	0	0	0			0
Total score	0	0	0	0	0	1	0	0	2	0	0	0	0	0	0	0	0	0
(N)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(0)	(12)	(12)	(12)	(12)	(12)	(12)	(12)	(0)	(0)	(12)

[a] pre-treatment; [b] day 8 of treatment; [c] lactation period

Urination [frequency/30sec]
Defecation [frequency/30sec]

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 6-1-4. Detailed clinical observations of female rats

SF 150/75 mg/kg

Female No.	Observations made while handling																		Open-field observations																	
	Behavior while removing from cage									Lacrimation									Vocalization									Touch response								
	Pre[a]	T8[b]	T15	T24	T30	T36	T42	T49	L[c]	Pre[a]	T8[b]	T15	T24	T30	T36	T42	T49	L[c]	Pre[a]	T8[b]	T15	T24	T30	T36	T42	T49	L[c]	Pre[a]	T8[b]	T15	T24	T30	T36	T42	T49	L[c]
F04037	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F04038	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F04039	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F04040	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F04041	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F04042	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F04043	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F04044	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F04045	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F04046	2	2	2	#	Died on day 26 of trreatment					2	2	2	#	Died on day 26 of trreatment					2	2	2	#	Died on day 26 of trreatment					2	2	2	#	Died on day 26 of trreatment				
F04047	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
F04048	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2
Total score	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0
(N)	(12)	(12)	(12)	(11)	(11)	(11)	(0)	(0)	(11)	(12)	(12)	(12)	(11)	(11)	(11)	(0)	(0)	(11)	(12)	(12)	(12)	(11)	(11)	(11)	(0)	(0)	(11)	(12)	(12)	(12)	(11)	(11)	(11)	(0)	(0)	(11)

[a] pre-treatment; [b] day 8 of treatment; [c] day 7 of recovery

Behavior while removing from cage [2, normal; 3, hard]

Lacrimation [2, not observed; 3, slight]

Vocalization [2, unheard; 3, heard]

Touch response [2, normal; 3, sensitive]

Data was excluded due to moribund state

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 6-1-4(continued). Detailed clinical observations of female rats

SF 150/75 mg/kg

Female No.	Open-field observations																	
	Urination									Defecation								
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	T49	L [c]	Pre	T8	T15	T24	T30	T36	T42	T49	L
F04037	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F04038	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F04039	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F04040	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F04041	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F04042	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F04043	1	0	0	2	1	0			0	0	0	0	1	1	0			0
F04044	0	0	0	0	0	1			2	0	0	0	0	0	0			0
F04045	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F04046	0	0	0	#	Died on day 26 of trreatment					0	0	0	#	Died on day 26 of trreatment				
F04047	0	0	0	0	0	0			0	0	0	0	0	0	0			0
F04048	0	0	0	0	0	0			0	0	0	0	0	0	0			0
Total score	1	0	0	2	1	1	0	0	2	0	0	0	1	1	0	0	0	0
(N)	(12)	(12)	(12)	(11)	(11)	(11)	(0)	(0)	(11)	(12)	(12)	(12)	(11)	(11)	(11)	(0)	(0)	(11)

[a] pre-treatment; [b] day 8 of treatment; [c] lactation period

Urination [frequency/30sec]

Defecation [frequency/30sec]

Data was excluded due to moribund state

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 6-2-1. Detailed clinical observations of female rats, satellite group

Control (vehicle: water for injection)

Female No.	Observations made while handling																		Open-field observations																	
	Behavior while removing from cage									Lacrimation									Vocalization									Touch response								
	Pre[a]	T8[b]	T15	T24	T30	T36	T42	R7[c]	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
F05049	2	2	2	2	2	2	2			2	2	2	3	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F05050	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F05051	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F05052	2	2	2	2	2	2	2			2	2	2	3	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F05053	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F05054	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05055	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05056	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05057	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F05058	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total score	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 2	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0
(N)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)

[a] pre-treatment; [b] day 8 of treatment; [c] day 7 of recovery

Behavior while removing from cage [2, normal; 3, hard]

Lacrimation [2, not observed; 3, slight]

Vocalization [2, unheard; 3, heard]

Touch response [2, normal; 3, sensitive]

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 6-2-1(continued). Detailed clinical observations of female rats, satellite group

Control (vehicle: water for injection)

Female No.	Open-field observations																	
	Urination									Defecation								
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	R7 [c]	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
F05049	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
F05050	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
F05051	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
F05052	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
F05053	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
F05054	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F05055	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F05056	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F05057	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F05058	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total score	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
(N)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)	(10)	(10)	(10)	(10)	(10)	(10)	(10)	(5)	(5)

[a] pre-treatment; [b] day 8 of treatment; [c] day 7 of recovery

Urination [frequency/30sec]

Defecation [frequency/30sec]

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 6-2-2. Detailed clinical observations of female rats, satellite group

SF 150/75 mg/kg

Female No.	Observations made while handling																			Open-field observations																				
	Behavior while removing from cage									Lacrimation									Vocalization									Touch response								
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	R7 [c]	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
F06059	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F06060	2	2	2	#	Died on day 25 of treatment					2	2	2	#	Died on day 25 of treatment					2	2	2	#	Died on day 25 of treatment					2	2	2	#	Died on day 25 of treatment				
F06061	2	2	2	Died on day 25 of treatment						2	2	2	Died on day 25 of treatment						2	2	2	Died on day 25 of treatment						2	2	2	Died on day 25 of treatment				
F06062	2	2	2	2	Died on day 28 of treatment					2	2	2	2	Died on day 28 of treatment					2	2	2	2	Died on day 28 of treatment					2	2	2	2	Died on day 28 of treatment				
F06063	2	2	2	Died on day 21 of treatment						2	2	2	Died on day 21 of treatment						2	2	2	Died on day 21 of treatment						2	2	2	Died on day 21 of treatment				
F06064	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F06065	2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2			2	2	2	2	2	2	2		
F06066	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F06067	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
F06068	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	3	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total score	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 1	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0	3: 0
(N)	(10)	(10)	(10)	(7)	(6)	(6)	(6)	(3)	(3)	(10)	(10)	(10)	(7)	(6)	(6)	(6)	(3)	(3)	(10)	(10)	(10)	(7)	(6)	(6)	(6)	(3)	(3)	(10)	(10)	(10)	(7)	(6)	(6)	(6)	(3)	(3)

[a] pre-treatment; [b] day 8 of treatment; [c] day 7 of recovery
Behavior while removing from cage [2, normal; 3, hard]
Lacrimation [2, not observed; 3, slight]
Vocalization [2, unheard; 3, heard]
Touch response [2, normal; 3, sensitive]
Data was excluded due to moribund state

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 6-2-2(continued). Detailed clinical observations of female rats, satellite group

SF 150/75 mg/kg

Female No.	Open-field observations																	
	Urination									Defecation								
	Pre [a]	T8 [b]	T15	T24	T30	T36	T42	R7 [c]	R14	Pre	T8	T15	T24	T30	T36	T42	R7	R14
F06059	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
F06060	0	0	0	#	Died on day 25 of treatment					0	0	0	#	Died on day 25 of treatment				
F06061	0	0	0	Died on day 25 of treatment						0	0	0	Died on day 25 of treatment					
F06062	0	0	0	0	Died on day 28 of treatment					0	0	0	0	Died on day 28 of treatment				
F06063	0	0	0	Died on day 21 of treatment						0	0	0	Died on day 21 of treatment					
F06064	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
F06065	0	0	0	0	0	0	0			0	0	0	0	0	0	0		
F06066	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
F06067	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
F06068	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0
Total score	0	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0	0
(N)	(10)	(10)	(10)	(7)	(6)	(6)	(6)	(3)	(3)	(10)	(10)	(10)	(7)	(6)	(6)	(6)	(3)	(3)

[a] pre-treatment; [b] day 8 of treatment; [c] day 7 of recovery

Urination [frequency/30sec]

Defecation [frequency/30sec]

Data was excluded due to moribund state

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 7-1-1. Body weights of male rats

Control (vehicle: water for injection)

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M01001	376.0	378.5	384.7	404.7	424.4	439.2	463.9	470.8
M01002	398.9	415.9	437.2	458.0	489.1	502.5	527.1	538.5
M01003	358.8	360.7	371.6	393.6	400.2	402.8	415.1	423.7
M01004	381.8	395.7	421.1	446.5	473.4	486.5	501.4	502.8
M01005	400.0	412.4	425.8	458.8	476.2	494.8	521.2	522.6
M01006	374.1	371.1	382.4	401.8	417.6	431.7	452.8	461.2
M01007	359.5	372.8	387.3	410.7	420.7	438.0	453.7	470.9
M01008	382.3	395.4	419.1	450.2	473.9	502.3	514.6	534.5
M01009	378.9	393.4	409.2	429.6	442.2	454.6	468.0	476.4
M01010	355.4	359.6	375.9	396.9	418.2	445.1	457.8	465.9
M01011	376.5	390.3	410.5	439.9	441.6	449.4	452.1	464.1
M01012	356.6	363.2	381.6	407.0	429.3	434.8	450.1	465.7
Number of males	12	12	12	12	12	12	12	12
Mean	374.9	384.1	400.5	424.8	442.2	456.8	473.2	483.1
S.D.	15.2	19.3	22.3	24.9	29.0	32.2	34.7	34.3

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 7-1-2. Body weights of male rats

SF 15 mg/kg

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M02013	366.1	357.8	367.6	372.4	407.6	425.0	447.8	423.7
M02014	377.0	383.7	396.0	412.0	420.7	422.6	439.2	439.6
M02015	380.4	396.6	418.0	457.9	471.8	485.7	495.7	509.3
M02016	367.0	379.6	391.2	419.0	443.2	467.2	493.6	509.5
M02017	398.1	404.4	405.5	426.9	457.0	489.9	515.4	526.2
M02018	396.4	409.4	425.8	454.0	471.5	483.9	500.7	509.1
M02019	356.1	362.0	386.9	408.7	415.3	431.1	447.5	466.4
M02020	366.5	372.0	385.3	414.8	439.4	451.7	469.1	470.2
M02021	334.5	350.9	358.6	370.8	390.4	405.3	406.4	424.0
M02022	386.2	397.4	407.4	431.2	446.0	461.1	482.2	496.3
M02023	372.4	385.0	399.0	421.9	440.7	471.8	488.6	489.6
M02024	355.9	375.1	400.8	421.6	442.9	456.7	474.7	493.0
Number of males	12	12	12	12	12	12	12	12
Mean	371.4	381.2	395.2	417.6	437.2	454.3	471.7	479.7
S.D.	18.0	18.6	19.2	26.3	24.8	27.7	31.2	35.0
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 7-1-3. Body weights of male rats

SF 50 mg/kg

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M03025	372.8	385.4	402.0	424.5	447.7	464.7	481.1	480.8
M03026	379.1	394.7	411.2	421.0	432.9	446.3	459.8	463.7
M03027	343.5	351.6	367.1	384.1	407.8	425.5	434.5	452.5
M03028	383.6	398.2	404.2	412.3	435.5	447.4	462.0	479.4
M03029	392.1	405.6	416.2	442.2	462.7	490.0	511.7	504.8
M03030	373.0	384.7	395.4	416.2	446.8	464.8	488.8	513.4
M03031	358.7	372.2	386.4	417.6	442.6	458.9	473.6	480.1
M03032	373.3	378.5	393.5	417.4	426.9	439.1	460.9	471.8
M03033	383.9	395.8	415.8	450.0	477.1	500.5	530.6	549.6
M03034	348.5	351.6	357.1	377.8	394.2	403.8	430.0	446.9
M03035	374.4	384.8	396.1	421.6	451.1	474.1	507.0	529.8
M03036	364.6	382.7	392.9	408.5	421.1	438.4	455.4	467.5
Number of males	12	12	12	12	12	12	12	12
Mean	370.6	382.2	394.8	416.1	437.2	454.5	474.6	486.7
S.D.	14.5	16.9	18.0	20.3	22.9	27.0	30.7	31.4
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 7-1-4. Body weights of male rats

SF 150/75 mg/kg

Male No.	Days of administration							
	1	4	7	14	21	28	35	42
M04037	375.6	393.1	402.7	428.2	455.4	472.7	489.8	487.2
M04038	383.2	379.4	401.7	434.4	456.1	478.4	511.1	525.2
M04039	384.1	396.7	413.9	441.3	455.8	466.6	490.2	496.9
M04040	377.9	385.9	390.4	399.2	426.2	440.9	464.2	469.9
M04041	373.1	380.7	390.2	426.2	445.3	461.8	480.3	467.7
M04042	364.6	366.8	370.6	390.4	416.0	426.3	455.4	450.1
M04043	399.0	414.4	423.6	453.4	473.2	503.7	522.2	546.1
M04044	369.7	374.0	385.9	403.5	432.4	455.9	485.2	504.4
M04045	347.1	349.4	351.5	367.8	385.4	398.6	424.5	421.0
M04046	361.4	360.8	372.5	334.5				
M04047	370.4	384.1	395.7	420.3	437.8	453.0	470.9	483.7
M04048	386.6	390.7	409.8	430.5	450.2	467.4	495.1	504.5
Number of males	12	12	12	12	11	11	11	11
Mean	374.4	381.3	392.4	410.8	439.4	456.8	480.8	487.0
S.D.	13.4	17.3	20.3	33.8	24.1	27.8	26.9	34.7
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 7-2-1. Body weights of male rats at the recovery period

Control (vehicle: water for injection)

Male No.	Days of recovery		
	1	7	14
M01008	539.3	552.6	565.8
M01009	480.0	496.0	508.0
M01010	468.1	479.4	496.1
M01011	465.0	487.4	499.0
M01012	461.1	479.3	491.9
Number of males	5	5	5
Mean	482.7	498.9	512.2
S.D.	32.4	30.8	30.6

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 7-2-2. Body weights of male rats at the recovery period

SF 150/75 mg/kg

Male No.	Days of recovery		
	1	7	14
M04043	547.6	560.5	536.8
M04044	502.3	513.7	497.7
M04045	417.9	432.0	437.4
M04047	483.8	501.6	470.7
M04048	509.6	528.4	504.6
Number of males	5	5	5
Mean	492.2	507.2	489.4
S.D.	47.6	47.5	37.4
Significance	NS	NS	NS
Statistical method	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 8-1-1. Body weights of female rats

Control (vehicle: water for injection)

Female No.	Days of administration								
	1	4	7	14	21	28	35	42	49
F01001	243.3	245.8	244.4	261.3					
F01002	237.6	246.2	252.1	253.2					
F01003	230.2	241.8	243.5	246.1					
F01004	227.1	232.1	242.9	250.1					
F01005	253.5	258.4	264.9	285.9					
F01006	245.5	241.7	255.7	269.9					
F01007	242.5	245.9	246.0	264.5					
F01008	250.6	257.0	261.9	279.2					
F01009	222.5	228.9	235.5	235.7					
F01010	225.6	225.5	234.1	243.4					
F01011	218.8	221.1	218.9	239.6	266.1	272.8	272.3	279.2	302.5
F01012	231.7	226.9	226.6	232.8					
Number of females	11	11	11	11					
Mean	237.3	240.9	246.1	256.6					
S.D.	10.5	11.4	11.8	17.2					

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 8-1-2. Body weights of female rats

SF 15 mg/kg

Female No.	Days of administration								
	1	4	7	14	21	28	35	42	49
F02013	256.3	253.7	258.6	279.5					
F02014	236.4	237.9	248.7	253.0					
F02015	236.0	245.5	248.9	256.3					
F02016	239.2	242.6	255.6	271.1					
F02017	220.1	219.8	225.8	224.8					
F02018	225.6	238.0	247.5	257.5					
F02019	251.6	265.3	259.6	277.0					
F02020	228.5	230.3	230.8	251.4					
F02021	251.4	250.7	253.9	266.2	294.0	305.7			
F02022	222.7	229.8	234.1	233.1					
F02023	232.3	239.5	244.4	254.5					
F02024	229.5	231.0	231.6	244.5					
Number of females	12	12	12	12					
Mean	235.8	240.3	245.0	255.7					
S.D.	11.9	12.3	11.7	16.5					
Significance	NS	NS	NS	NS					
Statistical method	AN	AN	AN	AN					

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 8-1-3. Body weights of female rats

SF 50 mg/kg

Female No.	Days of administration								
	1	4	7	14	21	28	35	42	49
F03025	219.1	232.8	245.4	253.1					
F03026	227.6	234.2	239.0	243.9					
F03027	217.6	225.9	230.0	233.2					
F03028	244.3	250.9	256.3	261.2					
F03029	241.9	246.9	250.3	248.1					
F03030	220.2	227.6	221.4	234.9					
F03031	223.0	230.6	240.0	249.3					
F03032	233.7	232.9	234.5	244.5					
F03033	230.8	233.7	246.6	258.6					
F03034	239.7	239.7	258.1	260.4					
F03035	251.3	264.9	278.1	292.6					
F03036	218.6	225.5	218.5	236.7					
Number of females	12	12	12	12					
Mean	230.7	237.1	243.2	251.4					
S.D.	11.5	11.7	16.6	16.1					
Significance	NS	NS	NS	NS					
Statistical method	AN	AN	AN	AN					

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 8-1-4. Body weights of female rats

SF 150/75 mg/kg

Female No.	Days of administration								
	1	4	7	14	21	28	35	42	49
F04037	225.4	243.8	253.7	262.3					
F04038	254.2	265.2	261.0	276.8					
F04039	222.9	226.7	230.4	230.4					
F04040	231.8	240.6	248.9	255.5					
F04041	228.1	226.5	225.0	233.1					
F04042	212.8	223.5	222.3	231.5					
F04043	257.8	259.1	264.1	270.3					
F04044	222.3	235.6	241.7	251.2					
F04045	226.0	243.7	252.1	256.4					
F04046	231.5	233.9	236.4	250.8					
F04047	230.4	247.2	244.8	255.9					
F04048	256.1	261.0	258.1	269.3					
Number of females	12	12	12	12					
Mean	233.3	242.2	244.9	253.6					
S.D.	14.7	14.0	14.0	15.4					
Significance	NS	NS	NS	NS					
Statistical method	AN	AN	AN	AN					

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 8-2-1. Body weights of female rats, satellite group

Control (vehicle: water for injection)

Female No.	Days of administration							
	1	4	7	14	21	28	35	42
F05049	244.0	247.3	257.3	261.9	270.9	282.1	286.8	284.1
F05050	232.1	245.2	251.2	257.6	257.1	267.7	277.5	275.9
F05051	230.9	241.8	251.1	263.3	267.7	280.2	289.8	291.9
F05052	225.7	233.4	238.4	247.0	252.4	259.8	268.1	264.8
F05053	227.6	224.3	236.4	239.8	245.0	246.1	254.9	253.3
F05054	236.4	240.1	249.5	266.1	267.3	269.5	276.2	288.5
F05055	253.9	258.7	269.9	272.0	288.1	294.8	307.5	307.4
F05056	253.6	257.8	264.9	282.2	289.2	293.2	294.8	297.2
F05057	231.3	235.8	233.2	244.0	251.1	249.4	246.4	255.2
F05058	229.5	240.0	252.3	255.3	258.2	267.6	275.3	280.4
Number of females	10	10	10	10	10	10	10	10
Mean	236.5	242.4	250.4	258.9	264.7	271.0	277.7	279.9
S.D.	10.4	10.5	11.9	13.1	15.0	16.7	18.3	17.8

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 8-2-2. Body weights of female rats, satellite group

SF 150/75 mg/kg

Female No.	Days of administration							
	1	4	7	14	21	28	35	42
F06059	214.0	225.2	228.9	236.8	238.2	248.1	248.4	246.7
F06060	242.2	242.6	256.0	262.4	251.1			
F06061	230.0	241.0	253.8	267.0	197.8			
F06062	243.8	244.1	240.5	259.7	281.0			
F06063	212.3	226.9	229.8	236.3				
F06064	239.1	243.2	248.0	265.8	278.3	274.1	272.3	277.5
F06065	239.7	247.6	247.2	255.7	261.0	268.5	271.6	271.2
F06066	235.4	237.4	240.9	251.4	255.6	253.3	294.9	280.9
F06067	235.4	233.6	240.7	252.3	255.7	258.8	265.2	277.2
F06068	247.2	258.7	261.9	264.2	285.2	291.9	289.6	289.0
Number of females	10	10	10	10	9	6	6	6
Mean	233.9	240.0	244.8	255.2	256.0	265.8	273.7	273.8
S.D.	12.0	9.9	10.8	11.2	26.8	16.0	16.9	14.5
Significance	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 8-3-1. Body weights of female rats at the recovery period

Control (vehicle: water for injection)

Female No.	Days of recovery		
	1	7	14
F05054	287.0	300.8	297.2
F05055	309.5	327.7	332.5
F05056	293.1	306.2	286.9
F05057	251.6	258.0	261.0
F05058	282.9	283.8	290.9
Number of females	5	5	5
Mean	284.8	295.3	293.7
S.D.	21.2	26.1	25.7

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 8-3-2. Body weights of female rats at the recovery period

SF 150/75 mg/kg

Female No.	Days of recovery		
	1	7	14
F06066	284.6	291.4	271.8
F06067	274.7	275.7	273.5
F06068	305.1	309.0	285.9
Number of females	3	3	3
Mean	288.1	292.0	277.1
S.D.	15.5	16.7	7.7
Significance	NS	NS	NS
Statistical method	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 9-1. Body weights of dams during pregnancy

Control (vehicle: water for injection)

Dam No.	Days of pregnancy			
	0	7	14	20
F01001	270.1	303.6	351.8	433.1
F01002	262.9	298.7	332.9	418.1
F01003	253.0	283.8	309.7	394.1
F01004	247.0	275.1	300.7	381.1
F01005	286.6	318.4	359.9	437.6
F01006	268.1	304.7	345.9	443.7
F01007	281.5	313.4	345.5	440.7
F01008	293.3	316.2	357.6	451.7
F01009	241.1	282.2	317.9	394.7
F01010	241.4	281.0	313.6	398.2
F01012	252.2	288.2	331.4	399.6
Number of dams	11	11	11	11
Mean	263.4	296.8	333.4	417.5
S.D.	18.2	15.5	20.5	24.8

>: Excluded from analysis (not pregnant)

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 9-2. Body weights of dams during pregnancy

SF 15 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F02013	275.9	324.0	368.7	457.3
F02014	255.0	302.8	339.8	421.0
F02015	260.4	288.4	319.8	413.0
F02016	278.9	306.6	350.3	435.0
F02017	233.2	259.2	292.7	368.2
F02018	265.4	295.4	323.9	410.9
F02019	291.4	340.2	373.6	437.8
F02020	267.0	286.0	322.0	403.3
F02021	302.3	319.4	336.4	420.3
F02022	240.3	270.6	307.1	405.5
F02023	264.1	299.9	336.4	410.4
F02024	252.6	289.4	319.9	388.8
Number of dams	12	12	12	12
Mean	265.5	298.5	332.6	414.3
S.D.	19.8	22.5	23.6	23.2
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN

>: Excluded from analysis (not pregnant)
Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 9-3. Body weights of dams during pregnancy

SF 50 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F03025	267.3	303.9	342.7	444.8
F03026	249.5	280.5	313.2	395.5
F03027	245.4	275.2	304.4	376.8
F03028	272.9	311.0	361.7	448.0
F03029	267.7	317.5	369.7	450.7
F03030	239.2	274.4	306.5	378.6
F03031	249.9	286.1	321.0	411.0
F03032	251.2	297.6	324.3	418.9
F03033	250.2	289.1	317.5	384.6
F03034	273.2	305.6	357.1	441.3
F03035	290.0	338.8	377.4	460.2
F03036	232.4	270.1	310.8	398.9
Number of dams	12	12	12	12
Mean	257.4	295.8	333.9	417.4
S.D.	16.7	20.5	26.4	30.6
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN

>: Excluded from analysis (not pregnant)

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 9-4. Body weights of dams during pregnancy

SF 150/75 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F04037	269.4	294.8	325.3	409.2
F04038	275.1	312.7	345.2	423.0
F04039	236.5	276.5	321.1	413.2
F04040	264.6	303.1	346.9	437.3
F04041	238.4	276.0	310.6	396.7
F04042	235.3	277.4	316.9	388.4
F04043	287.7	311.6	357.4	441.4
F04044	254.2	286.3	326.5	403.4
F04045	268.4	294.6	331.3	404.5
F04046	> 259.6	>	>	>
F04047	254.2	289.6	321.5	394.2
F04048	285.9	314.9	351.0	438.8
Number of dams	11	11	11	11
Mean	260.9	294.3	332.2	413.6
S.D.	18.8	14.7	15.5	18.9
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN

>: Excluded from analysis (not pregnant)

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 10-1. Body weights of dams during lactation

Control (vehicle: water for injection)

Dam No.	Days of lactation	
	0	4
F01001	333.5	342.7
F01002	297.7	321.3
F01003	287.0	304.0
F01004	294.2	295.0
F01005	336.3	354.8
F01006	324.4	328.8
F01007	324.4	323.1
F01008	320.6	363.5
F01009	287.9	317.1
F01010	288.7	309.3
F01012	329.8	324.5
Number of dams	11	11
Mean	311.3	325.8
S.D.	20.0	20.9

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 10-2. Body weights of dams during lactation

SF 15 mg/kg

Dam No.	Days of lactation	
	0	4
F02013	321.3	346.0
F02014	324.6	339.4
F02015	303.3	325.3
F02016	344.5	334.1
F02017	264.6	287.2
F02018	278.2	317.0
F02019	368.8	354.5
F02020	302.2	329.8
F02021	316.0	345.4
F02022	311.4	303.4
F02023	317.9	316.2
F02024	290.7	326.5
Number of dams	12	12
Mean	312.0	327.1
S.D.	28.0	19.1
Significance	NS	NS
Statistical method	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 10-3. Body weights of dams during lactation

SF 50 mg/kg

Dam No.	Days of lactation	
	0	4
F03025	346.0	324.1
F03026	321.8	314.1
F03027	300.4	307.8
F03028	341.0	340.6
F03029	341.1	347.2
F03030	297.2	307.3
F03031	300.6	322.9
F03032	313.1	322.1
F03033	299.2	310.0
F03034	352.3	343.7
F03035	375.8	377.5
F03036	299.0	314.4
Number of dams	12	12
Mean	324.0	327.6
S.D.	26.5	21.0
Significance	NS	NS
Statistical method	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 10-4. Body weights of dams during lactation

SF 150/75 mg/kg

Dam No.	Days of lactation	
	0	4
F04037	321.8	321.0
F04038	316.5	333.5
F04039	307.6	295.7
F04040	291.0	283.1
F04041	302.2	314.0
F04042	283.1	301.4
F04043	296.4	321.8
F04044	313.2	319.8
F04045	328.5	333.5
F04047	317.0	315.6
F04048	329.9	347.8
Number of dams	11	11
Mean	309.7	317.0
S.D.	15.2	18.4
Significance	NS	NS
Statistical method	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 11-1-1. Food consumption of male rats

Control (vehicle: water for injection)

Male No.	Days of administration					
	1	7	14	29	35	41
M01001	29.6	28.6	27.1	30.1	33.6	31.0
M01002	32.3	28.9	29.8	24.4	29.8	30.6
M01003	28.4	23.9	24.8	23.4	28.2	24.2
M01004	30.1	30.3	25.7	27.4	32.7	27.0
M01005	37.9	27.7	28.7	29.6	35.6	30.9
M01006	30.5	23.4	22.7	25.8	27.6	30.8
M01007	28.6	25.4	30.4	27.7	28.7	28.5
M01008	31.7	32.2	27.4	25.7	30.8	31.6
M01009	30.0	26.8	27.2	26.7	27.7	29.8
M01010	27.0	22.6	21.2	25.8	30.9	29.0
M01011	30.2	25.6	26.1	24.1	27.7	27.3
M01012	33.4	28.7	26.3	26.0	25.8	27.0
Number of males	12	12	12	12	12	12
Mean	30.8	27.0	26.5	26.4	29.9	29.0
S.D.	2.8	2.9	2.7	2.1	2.9	2.2

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 11-1-2. Food consumption of male rats

SF 15 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M02013	30.6	21.0	23.5	24.0	28.8	24.0
M02014	29.6	25.1	21.6	24.7	27.2	27.3
M02015	29.9	27.4	26.1	29.7	29.3	31.1
M02016	32.1	27.9	24.7	31.8	30.4	30.8
M02017	32.6	26.8	25.7	33.4	35.9	34.0
M02018	31.9	26.9	26.0	28.0	27.2	27.4
M02019	30.0	23.9	24.9	25.1	28.6	28.3
M02020	29.2	27.8	23.6	25.8	33.7	26.9
M02021	27.0	19.2	20.9	26.5	28.7	26.1
M02022	33.0	29.4	30.3	28.0	29.4	32.9
M02023	27.4	27.7	26.8	28.6	32.5	24.3
M02024	26.3	25.6	21.2	25.7	33.2	31.0
Number of males	12	12	12	12	12	12
Mean	30.0	25.7	24.6	27.6	30.4	28.7
S.D.	2.2	3.0	2.7	2.9	2.8	3.3
Significance	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	KW	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 11-1-3. Food consumption of male rats

SF 50 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M03025	29.9	25.8	25.8	27.7	31.3	28.2
M03026	30.5	27.6	26.4	24.9	32.6	28.8
M03027	20.8	24.6	24.9	26.0	30.0	29.0
M03028	28.3	24.6	21.5	23.4	27.7	28.9
M03029	36.6	28.4	29.2	29.9	32.6	31.7
M03030	29.6	25.4	25.9	27.6	32.4	28.4
M03031	28.5	27.2	24.8	23.0	26.9	24.4
M03032	33.9	30.2	29.5	28.9	29.2	28.2
M03033	35.6	30.3	33.0	30.2	37.2	35.4
M03034	26.6	24.9	26.5	25.6	32.0	29.4
M03035	25.0	28.8	28.4	29.9	34.0	29.7
M03036	31.8	31.1	24.4	27.4	28.6	24.4
Number of males	12	12	12	12	12	12
Mean	29.8	27.4	26.7	27.0	31.2	28.9
S.D.	4.5	2.4	3.0	2.5	2.9	2.9
Significance	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	KW	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 11-1-4. Food consumption of male rats

SF 150/75 mg/kg

Male No.	Days of administration					
	1	7	14	29	35	41
M04037	29.3	26.1	26.6	27.7	30.6	26.3
M04038	25.1	26.4	28.5	31.6	31.3	27.5
M04039	30.7	27.7	28.4	33.0	30.2	30.1
M04040	31.4	23.9	22.9	30.5	32.1	29.2
M04041	26.7	28.8	29.3	31.5	32.0	25.0
M04042	24.6	22.9	24.8	28.6	27.5	20.4
M04043	30.7	30.8	26.6	25.4	34.1	32.7
M04044	27.1	27.2	24.3	28.6	30.3	31.4
M04045	23.9	22.8	22.7	27.6	25.9	24.3
M04046	24.6	23.6	2.2			
M04047	28.9	28.1	27.5	28.5	30.6	28.2
M04048	27.7	25.2	24.4	26.2	28.5	29.5
Number of males	12	12	12	11	11	11
Mean	27.6	26.1	24.0	29.0	30.3	27.7
S.D.	2.6	2.5	7.2	2.4	2.3	3.5
Significance	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	KW	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 11-2-1. Food consumption of male rats at the recovery period

Control (vehicle: water for injection)

Male No.	Days of recovery	
	6	12
M01008	32.9	30.4
M01009	31.5	32.9
M01010	27.1	30.2
M01011	31.4	26.7
M01012	28.9	31.7
Number of males	5	5
Mean	30.4	30.4
S.D.	2.3	2.3

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 11-2-2. Food consumption of male rats at the recovery period

SF 150/75 mg/kg

Male No.	Days of recovery	
	6	12
M04043	32.0	30.9
M04044	25.8	27.9
M04045	20.8	25.8
M04047	30.9	28.0
M04048	32.6	28.7
Number of males	5	5
Mean	28.4	28.3
S.D.	5.0	1.8
Significance	NS	NS
Statistical method	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 12-1-1. Food consumption of female rats

Control (vehicle: water for injection)

Female No.	Days of administration						
	1	7	14	29	35	41	48
F01001	21.1	20.3	20.1				
F01002	17.8	20.7	22.5				
F01003	21.3	17.4	19.7				
F01004	22.3	22.3	22.4				
F01005	21.6	22.4	22.5				
F01006	22.7	14.9	19.7				
F01007	20.9	20.8	14.1				
F01008	22.8	23.5	16.6				
F01009	15.6	19.6	20.2				
F01010	20.5	16.0	19.3				
F01011	18.5	19.6	16.6	21.8	22.5	23.4	27.4
F01012	17.3	17.4	13.2				
Number of females	12	12	12				
Mean	20.2	19.6	18.9				
S.D.	2.3	2.7	3.1				

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 12-1-2. Food consumption of female rats

SF 15 mg/kg

Female No.	Days of administration						
	1	7	14	29	35	41	48
F02013	23.6	14.7	23.8				
F02014	19.3	15.7	19.0				
F02015	24.0	23.3	23.7				
F02016	21.5	18.7	20.8				
F02017	18.8	12.9	16.8				
F02018	20.9	20.2	23.2				
F02019	20.4	24.5	16.9				
F02020	20.0	18.4	17.6				
F02021	22.0	23.3	14.8				
F02022	16.8	20.5	19.2				
F02023	13.0	20.7	20.8				
F02024	19.4	19.3	17.1				
Number of females	12	12	12				
Mean	20.0	19.4	19.5				
S.D.	3.0	3.6	3.0				
Significance	NS	NS	NS				
Statistical method	AN	AN	AN				

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 12-1-3. Food consumption of female rats

SF 50 mg/kg

Female No.	Days of administration						
	1	7	14	29	35	41	48
F03025	21.9	20.3	22.2				
F03026	18.1	17.1	18.7				
F03027	20.0	20.1	17.4				
F03028	15.0	20.5	18.9				
F03029	16.4	18.9	16.0				
F03030	14.7	20.4	20.1				
F03031	21.0	18.5	23.6				
F03032	20.6	19.4	16.2				
F03033	21.4	14.0	19.9				
F03034	22.0	19.0	21.9				
F03035	24.0	25.7	28.5				
F03036	13.4	18.8	20.1				
Number of females	12	12	12				
Mean	19.0	19.4	20.3				
S.D.	3.4	2.7	3.5				
Significance	NS	NS	NS				
Statistical method	AN	AN	AN				

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 12-1-4. Food consumption of female rats

SF 150/75 mg/kg

Female No.	Days of administration						
	1	7	14	29	35	41	48
F04037	20.3	17.1	18.8				
F04038	17.9	21.5	22.5				
F04039	12.9	19.6	17.9				
F04040	19.7	18.1	20.2				
F04041	14.9	14.2	20.0				
F04042	19.3	17.9	19.6				
F04043	22.9	20.5	24.8				
F04044	20.1	18.4	21.3				
F04045	18.9	21.1	22.4				
F04046	18.5	18.8	17.4				
F04047	12.9	20.7	19.5				
F04048	24.8	21.2	20.7				
Number of females	12	12	12				
Mean	18.6	19.1	20.4				
S.D.	3.6	2.1	2.1				
Significance	NS	NS	NS				
Statistical method	AN	AN	AN				

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 12-2-1. Food consumption of female rats, satellite group

Control (vehicle: water for injection)

Female No.	Days of administration						
	1	7	14	21	29	35	41
F05049	17.5	20.9	18.8	17.6	17.6	20.6	15.1
F05050	20.0	20.7	24.2	20.0	21.6	21.7	18.5
F05051	21.6	20.5	23.5	21.9	20.8	22.1	19.8
F05052	17.1	18.1	16.8	20.3	19.1	21.8	14.0
F05053	22.0	14.4	20.6	21.1	21.5	16.5	12.5
F05054	21.3	15.1	18.9	23.3	21.0	18.3	22.6
F05055	22.2	19.5	20.3	21.5	13.0	23.9	17.0
F05056	21.8	22.3	16.0	25.8	10.6	20.6	20.7
F05057	18.8	20.3	16.2	16.8	32.5	20.6	20.1
F05058	23.5	20.8	22.0	21.7	20.6	23.6	23.5
Number of females	10	10	10	10	10	10	10
Mean	20.6	19.3	19.7	21.0	19.8	21.0	18.4
S.D.	2.1	2.6	2.9	2.6	5.8	2.2	3.7

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 12-2-2. Food consumption of female rats, satellite group

SF 150/75 mg/kg

Female No.	Days of administration						
	1	7	14	21	29	35	41
F06059	19.8	21.8	18.7	20.7	14.0	21.2	17.3
F06060	19.4	15.7	19.8	18.3			
F06061	18.6	20.3	23.4				
F06062	18.9	19.8	16.1	23.4			
F06063	20.3	18.6	18.4				
F06064	20.9	18.6	13.1	21.7	20.1	16.8	19.0
F06065	13.7	15.4	20.8	20.0	17.9	18.7	17.4
F06066	20.0	19.3	17.1	11.9	25.5	21.2	16.5
F06067	18.8	18.8	20.5	23.5	22.9	17.5	20.6
F06068	12.1	22.5	23.0	17.3	15.0	22.6	19.3
Number of females	10	10	10	8	6	6	6
Mean	18.3	19.1	19.1	19.6	19.2	19.7	18.4
S.D.	2.9	2.3	3.1	3.8	4.5	2.3	1.5
Significance	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 12-3-1. Food consumption of female rats at the recovery period

Control (vehicle: water for injection)

Female No.	Days of recovery	
	6	12
F05054	25.4	23.6
F05055	25.6	21.6
F05056	25.0	18.0
F05057	20.8	13.5
F05058	18.8	24.9
Number of females	5	5
Mean	23.1	20.3
S.D.	3.1	4.6

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 12-3-2. Food consumption of female rats at the recovery period

SF 150/75 mg/kg

Female No.	Days of recovery	
	6	12
F06066	19.2	16.7
F06067	19.4	18.8
F06068	25.0	19.9
Number of females	3	3
Mean	21.2	18.5
S.D.	3.3	1.6
Significance	NS	NS
Statistical method	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 13-1. Food consumption in dams during pregnancy

Control (vehicle: water for injection)

Dam No.	Days of pregnancy			
	0	7	14	20
F01001	21.6	28.6	27.4	24.3
F01002	21.2	24.7	26.2	20.4
F01003	23.3	22.4	24.1	22.2
F01004	18.7	21.9	24.6	25.4
F01005	22.0	27.6	29.7	27.5
F01006	20.5	25.1	31.1	28.1
F01007	24.4	28.0	28.1	24.5
F01008	22.6	25.3	27.3	23.3
F01009	19.9	24.7	25.6	20.5
F01010	20.6	27.2	28.9	22.9
F01012	18.8	26.5	26.6	23.9
Number of dams	11	11	11	11
Mean	21.2	25.6	27.2	23.9
S.D.	1.8	2.2	2.1	2.5

>: Excluded from analysis (not pregnant)

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 13-2. Food consumption in dams during pregnancy

SF 15 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F02013	24.0	28.3	32.1	31.8
F02014	21.0	26.0	28.0	30.6
F02015	23.0	24.8	28.6	29.7
F02016	23.6	27.1	28.8	26.6
F02017	19.2	23.4	22.0	23.1
F02018	22.2	24.1	23.6	16.3
F02019	28.4	36.5	30.3	19.4
F02020	21.9	25.5	27.7	28.4
F02021	21.2	22.2	22.8	26.5
F02022	20.1	23.5	24.0	18.0
F02023	19.5	29.8	27.6	25.6
F02024	25.1	23.4	16.8	21.1
Number of dams	12	12	12	12
Mean	22.4	26.2	26.0	24.8
S.D.	2.6	3.9	4.3	5.1
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN

>: Excluded from analysis (not pregnant)
Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 13-3. Food consumption in dams during pregnancy

SF 50 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F03025	23.9	25.3	29.6	24.6
F03026	17.8	19.6	25.6	25.6
F03027	17.4	25.9	24.8	19.9
F03028	18.8	31.7	29.3	26.4
F03029	23.4	32.4	32.6	22.7
F03030	19.1	28.0	26.7	28.9
F03031	22.7	26.5	29.0	30.2
F03032	20.4	25.0	29.5	24.6
F03033	20.2	27.1	25.7	26.4
F03034	19.8	31.4	30.6	25.7
F03035	19.6	31.3	32.6	31.8
F03036	16.3	25.2	34.7	26.5
Number of dams	12	12	12	12
Mean	20.0	27.5	29.2	26.1
S.D.	2.4	3.7	3.1	3.2
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN

>: Excluded from analysis (not pregnant)
Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 13-4. Food consumption in dams during pregnancy

SF 150/75 mg/kg

Dam No.	Days of pregnancy			
	0	7	14	20
F04037	19.6	22.8	24.9	28.4
F04038	23.4	23.5	26.3	24.3
F04039	17.1	26.8	25.0	19.5
F04040	22.5	27.3	33.9	16.0
F04041	22.6	25.9	28.2	25.1
F04042	22.4	29.5	31.0	19.9
F04043	20.3	26.0	27.4	20.1
F04044	23.2	27.6	26.7	24.1
F04045	25.1	23.9	25.6	24.1
F04046	> 19.7 >	>	>	>
F04047	19.4	22.6	28.1	30.3
F04048	22.2	32.4	31.5	25.8
Number of dams	11	11	11	11
Mean	21.6	26.2	28.1	23.4
S.D.	2.3	3.0	2.9	4.2
Significance	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN

>: Excluded from analysis (not pregnant)

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 14-1. Food consumption in dams during lactation

Control (vehicle: water for injection)

Dam No.	Days of lactation
	3
F01001	41.5
F01002	46.8
F01003	41.5
F01004	44.3
F01005	43.3
F01006	37.1
F01007	42.1
F01008	54.3
F01009	40.1
F01010	40.9
F01012	43.0
Number of dams	11
Mean	43.2
S.D.	4.4

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 14-2. Food consumption in dams during lactation

SF 15 mg/kg

Dam No.	Days of lactation
	3
F02013	35.9
F02014	39.3
F02015	44.9
F02016	38.5
F02017	37.5
F02018	53.1
F02019	38.2
F02020	55.2
F02021	43.2
F02022	45.0
F02023	39.0
F02024	49.2
Number of dams	12
Mean	43.3
S.D.	6.4
Significance	NS
Statistical method	KW

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 14-3. Food consumption in dams during lactation

SF 50 mg/kg

Dam No.	Days of lactation
	3
F03025	41.3
F03026	43.2
F03027	43.6
F03028	38.0
F03029	40.5
F03030	41.7
F03031	48.8
F03032	50.3
F03033	37.1
F03034	42.0
F03035	46.7
F03036	45.0
Number of dams	12
Mean	43.2
S.D.	4.0
Significance	NS
Statistical method	KW

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 14-4. Food consumption in dams during lactation

SF 150/75 mg/kg

Dam No.	Days of lactation
	3
F04037	41.7
F04038	46.4
F04039	38.4
F04040	19.2
F04041	46.5
F04042	40.4
F04043	30.1
F04044	49.2
F04045	48.4
F04047	39.6
F04048	51.9
Number of dams	11
Mean	41.1
S.D.	9.5
Significance	NS
Statistical method	KW

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 15-1. Functional findings of male rats at the end of the dosing period

Cotrol (vehicle: water for injection)
Male

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
M01001	2	2	2	2	+	+	+
M01002	2	2	2	2	+	+	+
M01003	2	2	2	2	+	+	+
M01004	2	2	2	2	+	+	+
M01005	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

SF (15 mg/kg)
Male

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
M02013	2	2	2	2	+	+	+
M02014	2	2	2	2	+	+	+
M02015	2	2	2	2	+	+	+
M02016	2	2	2	2	+	+	+
M02017	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 15-2. Functional findings of male rats at the end of the dosing period

SF (50 mg/kg)
Male

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
M03025	2	2	2	2	+	+	+
M03026	2	2	2	2	+	+	+
M03027	2	2	2	2	+	+	+
M03028	2	2	2	2	+	+	+
M03029	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

SF (150/75 mg/kg)
Male

Male No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
M04037	2	2	2	2	+	+	+
M04038	2	2	2	2	+	+	+
M04039	2	2	2	2	+	+	+
M04040	2	2	2	2	+	+	+
M04041	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 16-1. Functional findings of female rats at the end of the dosing period

Control (vehicle: water for injection)
Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F01003	2	2	2	2	+	+	+
F01004	2	2	2	2	+	+	+
F01005	2	2	2	2	+	+	+
F01006	2	2	2	2	+	+	+
F01010	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

SF (15 mg/kg)
Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F02013	2	2	2	2	+	+	+
F02014	2	2	2	2	+	+	+
F02015	2	2	2	2	+	+	+
F02016	2	2	2	2	+	+	+
F02017	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 16-2. Functional findings of female rats at the end of the dosing period

SF (50 mg/kg)
Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F03025	2	2	2	2	+	+	+
F03026	2	2	2	2	+	+	+
F03030	2	2	2	2	+	+	+
F03033	2	2	2	2	+	+	+
F03036	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

SF (150/75 mg/kg)
Female, dam

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F04037	2	2	2	2	+	+	+
F04038	2	2	2	2	+	+	+
F04041	2	2	2	2	+	+	+
F04042	2	2	2	2	+	+	+
F04047	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 16-3. Functional findings of female rats , satellite group

Control (vehicle: water for injection)
Female, satelite group

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F05049	2	2	2	2	+	+	+
F05050	2	2	2	2	+	+	+
F05051	2	2	2	2	+	+	+
F05052	2	2	2	2	+	+	+
F05053	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

SF (150/75 mg/kg)
Female, satelite group

Female No.	Righting reflex	Visual placing	Pupillary reflex	Startle reaction	Preyer's reaction	Withdrawal reflex	Eyelid reflex
F06059	2	2	2	2	+	+	+
F06064	2	2	2	2	+	+	+
F06065	2	2	2	2	+	+	+
F06066	2	2	2	2	+	+	+
F06067	2	2	2	2	+	+	+
Total	2: 5	2: 5	2: 5	2: 5	+: 5	+: 5	+: 5

2 or +, normal

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 17. Assessment of grip strength of male rats

Control (vehicle: water for injection)

Male No.	Administration period	
	Forelimb (kg)	Hindlimb (kg)
M01001	1.025	0.746
M01002	1.247	0.847
M01003	1.137	0.944
M01004	1.147	0.980
M01005	1.142	0.839
Number of males	5	5
Mean	1.140	0.871
S.D.	0.079	0.093

SF (50 mg/kg)

Male No.	Administration period	
	Forelimb (kg)	Hindlimb (kg)
M03025	1.192	0.892
M03026	1.115	0.833
M03027	1.094	0.686
M03028	1.130	0.814
M03029	1.099	0.824
Number of males	5	5
Mean	1.126	0.810
S.D.	0.040	0.076

SF (15 mg/kg)

Male No.	Administration period	
	Forelimb (kg)	Hindlimb (kg)
M02013	1.153	0.704
M02014	1.192	0.873
M02015	1.158	0.879
M02016	1.203	0.913
M02017	0.992	0.842
Number of males	5	5
Mean	1.140	0.842
S.D.	0.085	0.081

SF(150/75 mg/kg)

Male No.	Administration period	
	Forelimb (kg)	Hindlimb (kg)
M04037	1.106	0.923
M04038	1.050	0.921
M04039	1.110	0.846
M04040	1.171	0.895
M04041	1.222	0.910
Number of males	5	5
Mean	1.132	0.899
S.D.	0.066	0.032

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 18. Assessment of grip strength of female rats

Control (vehicle: water for injection)

Female No.	Administration period	
	Forelimb (kg)	Hindlimb (kg)
F01003	1.003	0.724
F01004	1.249	0.751
F01005	0.991	0.784
F01006	1.251	0.683
F01010	1.098	0.803
Number of females	5	5
Mean	1.118	0.749
S.D.	0.127	0.048

SF (50 mg/kg)

Female No.	Administration period	
	Forelimb (kg)	Hindlimb (kg)
F03025	1.186	0.747
F03026	1.082	0.607
F03030	1.017	0.672
F03033	1.228	0.748
F03036	1.070	0.721
Number of females	5	5
Mean	1.117	0.699
S.D.	0.087	0.060

SF (15 mg/kg)

Female No.	Administration period	
	Forelimb (kg)	Hindlimb (kg)
F02013	1.077	0.944
F02014	1.086	0.714
F02015	0.976	0.685
F02016	1.086	0.686
F02017	1.018	0.651
Number of females	5	5
Mean	1.049	0.736
S.D.	0.050	0.118

SF (150/75 mg/kg)

Female No.	Administration period	
	Forelimb (kg)	Hindlimb (kg)
F04037	1.156	0.689
F04038	1.309	0.503
F04041	1.095	0.551
F04042	1.116	0.812
F04047	1.034	0.718
Number of females	5	5
Mean	1.142	0.655
S.D.	0.103	0.126

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 19. Assessment of grip strength of female rats, satellite group

Control (vehicle: water for injection)

Female No.	Administration period	
	Forelimb (kg)	Hindlimb (kg)
F05049	1.097	0.657
F05050	1.093	0.807
F05051	1.121	0.867
F05052	1.188	0.686
F05053	1.086	0.831
Number of females	5	5
Mean	1.117	0.770
S.D.	0.042	0.093

SF (150/75 mg/kg)

Female No.	Administration period	
	Forelimb (kg)	Hindlimb (kg)
F06059	1.112	0.811
F06064	1.195	0.911
F06065	1.253	0.693
F06066	1.042	0.699
F06067	1.187	0.795
Number of females	5	5
Mean	1.158	0.782
S.D.	0.082	0.090

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 20-1. Motor activity of male rats

Control (vehicle: water for injection)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M01001	1056	974	883	789	3702	37	22	36	10	105
M01002	1134	1056	911	319	3420	40	27	28	9	104
M01003	1075	1121	1094	893	4183	37	31	24	10	102
M01004	1230	1246	999	669	4144	34	25	16	23	98
M01005	1389	1380	1311	1085	5165	40	39	40	30	149
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1177	1155	1040	751	4123	38	29	29	16	112
S.D.	137	160	173	286	664	3	7	10	10	21

SF (15 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M02013	1100	875	694	54	2723	31	20	17	0	68
M02014	997	1089	1015	932	4033	31	30	30	36	127
M02015	1439	1217	1286	1275	5217	58	40	40	43	181
M02016	1074	1072	1100	900	4146	35	21	28	9	93
M02017	1285	1340	1180	978	4783	37	35	22	25	119
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1179	1119	1055	828	4180	38	29	27	23	118
S.D.	180	174	225	458	947	11	9	9	18	42

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 20-2. Motor activity of male rats

SF (50 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M03025	996	1205	697	667	3565	28	32	11	13	84
M03026	1174	1157	854	660	3845	35	25	12	25	97
M03027	824	793	720	382	2719	37	38	29	13	117
M03028	1205	984	1121	1002	4312	42	18	31	23	114
M03029	1200	1012	736	995	3943	46	38	21	29	134
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1080	1030	826	741	3677	38	30	21	21	109
S.D.	167	162	176	262	598	7	9	9	7	19

SF (150/75 mg/kg)

Male No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
M04037	1744	1719	1465	1103	6031	29	15	14	9	67
M04038	986	798	661	204	2649	26	15	16	1	58
M04039	1101	823	383	429	2736	41	18	6	3	68
M04040	1378	1084	707	559	3728	42	21	11	13	87
M04041	884	814	920	628	3246	28	26	23	13	90
Number of males	5	5	5	5	5	5	5	5	5	5
Mean	1219	1048	827	585	3678	33	19	14	8	74
S.D.	347	394	405	332	1385	8	5	6	6	14

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 21-1. Motor activity of female rats

Ccontrol (vehicle: water for injection)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F01003	979	514	217	357	2067	22	6	0	0	28
F01004	973	550	623	401	2547	20	5	0	0	25
F01005	1054	890	451	465	2860	27	17	12	4	60
F01006	870	238	384	8	1500	16	7	5	0	28
F01010	689	388	354	424	1855	40	33	18	12	103
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	913	516	406	331	2166	25	14	7	3	49
S.D.	141	242	148	185	542	9	12	8	5	34

SF (15 mg/kg)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F02013	1056	876	499	323	2754	27	9	13	4	53
F02014	1084	608	529	414	2635	29	10	4	2	45
F02015	1189	848	543	420	3000	31	10	0	9	50
F02016	1061	794	145	529	2529	24	12	0	11	47
F02017	1127	915	670	341	3053	32	17	7	3	59
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1103	808	477	405	2794	29	12	5	6	51
S.D.	55	120	197	81	227	3	3	5	4	5

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 21-2. Motor activity of female rats

SF (50 mg/kg)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F03025	1050	1025	732	829	3636	30	12	6	6	54
F03026	1175	754	413	621	2963	34	18	1	15	68
F03030	1083	1012	867	444	3406	24	18	13	11	66
F03033	1042	863	171	477	2553	30	26	2	4	62
F03036	1192	986	896	800	3874	31	15	12	4	62
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1108	928	616	634	3286	30	18	7	8	62
S.D.	71	117	314	178	530	4	5	6	5	5

SF (150/75 mg/kg)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F04037	904	901	599	916	3320	35	23	15	17	90
F04038	1258	650	400	325	2633	29	4	2	1	36
F04041	1399	609	771	231	3010	29	6	12	0	47
F04042	1553	1555	1127	984	5219	21	27	9	5	62
F04047	1129	718	708	340	2895	36	9	10	1	56
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1249	887	721	559	3415	30	14	10	5	58
S.D.	249	390	267	360	1038	6	10	5	7	20

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 22-1. Motor activity of female rats, satellite group

Control (vehicle: water for injection)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F05049	1144	1064	942	817	3967	32	40	20	16	108
F05050	1037	1112	1085	1057	4291	25	30	54	32	141
F05051	1311	1395	1092	1217	5015	58	63	37	65	223
F05052	1024	687	680	834	3225	30	13	8	26	77
F05053	1151	810	540	639	3140	27	15	6	6	54
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1133	1014	868	913	3928	34	32	25	29	121
S.D.	115	277	248	226	779	13	20	20	22	66

SF (150/75 mg/kg)

Female No.	Administration period									
	Ambulation (counts)					Rearing (counts)				
	5min	10min	15min	20min	Total	5min	10min	15min	20min	Total
F06059	1226	1254	1179	1130	4789	38	30	28	17	113
F06064	1040	979	961	971	3951	33	24	32	37	126
F06065	1241	1214	1218	1335	5008	31	37	39	50	157
F06066	1076	1053	978	910	4017	35	35	34	29	133
F06067	1218	978	826	148	3170	42	35	23	4	104
Number of females	5	5	5	5	5	5	5	5	5	5
Mean	1160	1096	1032	899	4187	36	32	31	27	127
S.D.	95	131	163	451	734	4	5	6	18	20

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 23-1-1. Urinalysis in male rats

Control (vehicle: water for injection)

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M01001	Light yellow	-	7.0	2+	-	±	-	-	±	-	-	-	±	-
M01002	Light yellow	-	7.0	+	-	±	-	-	±	-	-	-	±	-
M01003	Light yellow	-	7.5	+	-	-	-	-	±	-	-	-	±	-
M01004	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	-	-
M01005	Light yellow	-	7.5	+	-	±	-	-	±	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M01001	12.7	1.074	133.8	217.0	169.1	1.70	2.76	2.15
M01002	14.0	1.062	81.0	194.2	118.7	1.13	2.72	1.66
M01003	15.1	1.055	95.1	171.9	112.7	1.44	2.60	1.70
M01004	30.0	1.031	42.3	117.9 §	54.0	1.27	3.54	1.62
M01005	19.8	1.050	97.5	161.4	100.8	1.93	3.20	2.00
Number of males	5	5	5	5	5	5	5	5
Mean	18.3	1.054	89.9	172.5	111.1	1.49	2.96	1.83
±S.D.	7.1	0.016	33.0	37.3	41.2	0.32	0.39	0.24

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.
Turbidity, -: negative
Protein, ±: 10≦and＜30 mg/dL; +: 30≦and＜100 mg/dL; 2+: 100≦and＜300 mg/dL
Glucose, -: negative
Ketone, -: negative; ±: 5≦and＜10 mg/dL; +: 10≦and＜40 mg/dL; 2+: 40≦and＜80 mg/dL
Bilirubin, -: negative
Occult blood, -: negative
Urobilinogen, ±: normal; +: 2.0≦and＜4.0 mg/dL; 2+: 4.0≦and＜8.0 mg/dL
Red blood cells, White blood cells and Casts, -: not observed
Crystals and Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 23-1-2. Urinalysis in male rats

SF (15 mg/kg)

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M02013	Light yellow	-	6.0	+	-	±	-	-	±	-	-	-	-	-
M02014	Light yellow	-	6.5	+	-	+	-	-	+	-	-	-	±	-
M02015	Light yellow	-	7.0	+	-	±	-	-	±	-	-	-	±	-
M02016	Light yellow	-	7.0	+	-	-	-	-	±	-	-	-	±	-
M02017	Light yellow	-	7.0	±	-	±	-	-	±	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyt		
			Na	K	Cl	Na	K	Cl
M02013	11.0	1.070	134.9	164.7	158.4	1.48	1.81	1.74
M02014	11.3	1.070	128.6	215.4 §	138.7	1.45	2.43	1.57
M02015	15.4	1.055	127.5	148.4	100.8	1.96	2.29	1.55
M02016	22.8	1.044	90.0	146.2	105.0	2.05	3.33	2.39
M02017	15.9	1.063	100.5	173.4	137.2	1.60	2.76	2.18
Number of males	5	5	5	5	5	5	5	5
Mean	15.3	1.060	116.3	169.6	128.0	1.71	2.52	1.89
±S.D.	4.8	0.011	19.8	28.0	24.5	0.28	0.57	0.38

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.
Significantly different from the control group (*: P<0.05, **: P<0.01).
Turbidity, -: negative
Protein, ±: 10≦and<30 mg/dL; +: 30≦and<100 mg/dL; 2+: 100≦and<300 mg/dL
Glucose, -: negative
Ketone, -: negative; ±: 5≦and<10 mg/dL; +: 10≦and<40 mg/dL; 2+: 40≦and<80 mg/dL
Bilirubin, -: negative
Occult blood, -: negative
Urobilinogen, ±: normal; +: 2.0≦and<4.0 mg/dL; 2+: 4.0≦and<8.0 mg/dL
Red blood cells, White blood cells and Casts, -: not observed
Crystals and Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 23-1-3. Urinalysis in male rats

SF (50 mg/kg)

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M03025	Light yellow	-	6.0	+	-	±	-	-	±	-	-	-	±	-
M03026	Light yellow	-	6.5	+	-	±	-	-	±	-	-	-	-	-
M03027	Light yellow	-	6.0	+	-	±	-	-	±	-	-	-	-	-
M03028	Light yellow	-	6.0	+	-	+	-	-	+	-	-	-	-	-
M03029	Light yellow	-	6.5	+	-	-	-	-	±	-	-	-	-	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyt		
			Na	K	Cl	Na	K	Cl
M03025	19.8	1.049	57.5	128.5	94.8	1.14	2.54	1.88
M03026	16.5	1.057	90.1	157.2	99.8	1.49	2.59	1.65
M03027	17.4	1.056	92.6	163.4	106.7	1.61	2.84	1.86
M03028	13.0	1.074	120.8	201.1 §	142.4	1.57	2.61	1.85
M03029	25.6	1.042	85.8	130.3 §	94.5	2.20	3.34	2.42
Number of males	5	5	5	5	5	5	5	5
Mean	18.5	1.056	89.4	156.1	107.6	1.60	2.78	1.93
±S.D.	4.7	0.012	22.5	29.6	20.1	0.38	0.33	0.29

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.
Significantly different from the control group (*: P<0.05, **: P<0.01).
Turbidity, -: negative
Protein, ±: 10≦and<30 mg/dL; +: 30≦and<100 mg/dL; 2+: 100≦and<300 mg/dL
Glucose, -: negative
Ketone, -: negative; ±: 5≦and<10 mg/dL; +: 10≦and<40 mg/dL; 2+: 40≦and<80 mg/dL
Bilirubin, -: negative
Occult blood, -: negative
Urobilinogen, ±: normal; +: 2.0≦and<4.0 mg/dL; 2+: 4.0≦and<8.0 mg/dL
Red blood cells, White blood cells and Casts, -: not observed
Crystals and Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 23-1-4. Urinalysis in male rats

SF (150/75 mg/kg)

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M04037	Light yellow	-	6.5	+	-	±	-	-	±	-	-	-	±	-
M04038	Light yellow	-	6.5	+	-	±	-	-	+	-	-	-	±	±
M04039	Light yellow	-	6.5	+	-	±	-	-	+	-	-	-	±	-
M04040	Light yellow	-	6.5	+	-	±	-	-	±	-	-	-	±	-
M04041	Light yellow	-	6.5	+	-	-	-	-	±	-	-	-	-	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyt		
			Na	K	Cl	Na	K	Cl
M04037	15.9	1.059	152.7	194.9	125.4	2.43	3.10	1.99
M04038	26.1	1.041	91.0	141.5	84.5	2.38	3.69	2.21
M04039	16.5	1.058	131.1	172.7	112.2	2.16	2.85	1.85
M04040	16.9	1.062	149.1	195.9 §	126.3	2.52	3.31	2.13
M04041	18.6	1.035	49.2	113.3 §	18.9	0.92	2.11	0.35
Number of males	5	5	5	5	5	5	5	5
Mean	18.8	1.051	114.6	163.7	93.5	2.08	3.01	1.71
±S.D.	4.2	0.012	44.0	35.8	45.0	0.66	0.59	0.77

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.
Significantly different from the control group (*: P<0.05, **: P<0.01).
Turbidity, -: negative
Protein, ±: 10≦and<30 mg/dL; +: 30≦and<100 mg/dL; 2+: 100≦and<300 mg/dL
Glucose, -: negative
Ketone, -: negative; ±: 5≦and<10 mg/dL; +: 10≦and<40 mg/dL; 2+: 40≦and<80 mg/dL
Bilirubin, -: negative
Occult blood, -: negative
Urobilinogen, ±: normal; +: 2.0≦and<4.0 mg/dL; 2+: 4.0≦and<8.0 mg/dL
Red blood cells, White blood cells and Casts, -: not observed
Crystals and Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 23-2-1. Urinalysis in male rats of the recovery period

Ccontrol (vehicle: water for injection)

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M01008	Light yellow	-	6.5	2+	-	+	-	-	+	-	-	-	±	-
M01009	Light yellow	-	7.5	+	-	±	-	-	±	-	-	-	+	-
M01010	Light yellow	-	8.5	+	-	±	-	-	±	-	-	-	±	-
M01011	Light yellow	-	7.0	+	-	+	-	±	±	-	-	-	±	-
M01012	Light yellow	-	7.5	+	-	±	-	-	+	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M01008	15.4	1.072	132.6	251.0 §	158.7	2.04	3.87	2.44
M01009	13.7	1.074	158.8	271.1 §	187.7	2.18	3.71	2.57
M01010	15.2	1.062	109.9	217.6 §	124.7	1.67	3.31	1.90
M01011	18.8	1.050	97.7	198.3 §	105.4	1.84	3.73	1.98
M01012	15.3	1.065	99.5	225.5	127.7	1.52	3.45	1.95
Number of males	5	5	5	5	5	5	5	5
Mean	15.7	1.065	119.7	232.7	140.8	1.85	3.61	2.17
±S.D.	1.9	0.010	25.9	28.6	32.4	0.27	0.23	0.31

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.
Turbidity, -: negative
Protein, ±: 10≦and＜30 mg/dL; +: 30≦and＜100 mg/dL; 2+: 100≦and＜300 mg/dL
Glucose, -: negative
Ketone, -: negative; ±: 5≦and＜10 mg/dL; +: 10≦and＜40 mg/dL; 2+: 40≦and＜80 mg/dL
Bilirubin, -: negative
Occult blood, -: negative
Urobilinogen, ±: normal; +: 2.0≦and＜4.0 mg/dL; 2+: 4.0≦and＜8.0 mg/dL
Red blood cells, White blood cells and Casts, -: not observed
Crystals and Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 23-2-2. Urinalysis in male rats of the recovery period

SF (150/75 mg/kg)

Male No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
M04043	Light yellow	-	7.0	+	-	±	-	-	+	-	-	-	±	-
M04044	Light yellow	-	7.0	+	-	+	-	-	+	-	-	-	±	-
M04045	Light yellow	-	7.5	+	-	±	-	-	+	-	-	-	±	-
M04047	Light yellow	-	7.0	2+	-	+	-	-	+	-	-	-	+	-
M04048	Light yellow	-	6.5	2+	-	+	-	-	2+	-	-	-	±	-

Male No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
M04043	12.6	1.053	69.0	182.1	60.6	0.87	2.29	0.76
M04044	10.1	1.066	86.8	182.3 §	73.2	0.88	1.84	0.74
M04045	13.3	1.058	112.6	227.7 §	129.8	1.50	3.03	1.73
M04047	7.4	1.074	115.9	213.1 §	86.6	0.86	1.58	0.64
M04048	7.8	1.077	99.0	212.9 §	52.6	0.77	1.66	0.41
Number of males	5	5	5	5	5	5	5	5
Mean	10.2 **	1.066	96.7	203.6	80.6 *	0.98 **	2.08 **	0.86 **
±S.D.	2.7	0.010	19.3	20.5	30.4	0.30	0.60	0.51

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.
Significantly different from the control group (*: P<0.05, **: P<0.01).
Turbidity, -: negative
Protein, ±: 10≦and<30 mg/dL; +: 30≦and<100 mg/dL; 2+: 100≦and<300 mg/dL
Glucose, -: negative
Ketone, -: negative; ±: 5≦and<10 mg/dL; +: 10≦and<40 mg/dL; 2+: 40≦and<80 mg/dL
Bilirubin, -: negative
Occult blood, -: negative
Urobilinogen, ±: normal; +: 2.0≦and<4.0 mg/dL; 2+: 4.0≦and<8.0 mg/dL
Red blood cells, White blood cells and Casts, -: not observed
Crystals and Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 24-1-1. Urinalysis in female rats, satellite group

Control (vehicle: water for injection)

Female No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F05049	Light yellow	-	6.5	-	-	-	-	-	±	-	-	-	-	-
F05050	Light yellow	-	6.0	+	-	+	-	-	+	-	-	-	±	-
F05051	Light yellow	-	7.0	-	-	-	-	-	±	-	-	-	±	-
F05052	Light yellow	-	7.0	±	-	-	-	-	±	-	-	-	±	-
F05053	Light yellow	-	7.0	-	-	-	-	-	±	-	-	-	±	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F05049	9.3	1.064	129.6	195.3 §	123.8	1.21	1.82	1.15
F05050	5.2	1.067	111.4	168.5 §	107.0	0.58	0.88	0.56
F05051	14.3	1.048	75.7	162.8	93.1	1.08	2.33	1.33
F05052	9.0	1.060	77.0	167.7 §	86.8	0.69	1.51	0.78
F05053	10.4	1.061	109.8	186.2 §	136.6	1.14	1.94	1.42
Number of females	5	5	5	5	5	5	5	5
Mean	9.6	1.060	100.7	176.1	109.5	0.94	1.70	1.05
±S.D.	3.3	0.007	23.6	13.9	20.8	0.28	0.54	0.37

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.
Turbidity, -: negative
Protein, -: negative; ±: 10≦and＜30 mg/dL; +: 30≦and＜100 mg/dL
Glucose, -: negative
Ketone, -: negative; ±: 5≦and＜10 mg/dL; +: 10≦and＜40 mg/dL
Bilirubin, -: negative
Occult blood, -: negative
Urobilinogen, ±: normal; +: 2.0≦and＜4.0 mg/dL
Red blood cells, White blood cells and Casts, -: not observed
Crystals and Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 24-1-2. Urinalysis in female rats, satellite group

SF (150/75 mg/kg)

Female No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells	White blood cells	Casts	Crystals	Epithelial cells
F06059	Light yellow	-	6.0	-	-	-	-	-	±	-	-	-	-	-
F06064	Light yellow	-	6.5	±	-	-	-	-	±	-	-	-	-	-
F06065	Light yellow	+	6.0	2+	-	±	-	-	±	-	-	-	-	±
F06066	Light yellow	-	5.5	-	-	-	-	-	±	-	-	-	-	-
F06067	Light yellow	-	6.0	-	-	-	-	-	±	-	-	-	-	±

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F06059	11.6	1.029	51.0	89.8 §	25.3	0.59	1.04	0.29
F06064	14.7	1.029	52.1	94.4	18.6	0.77	1.39	0.27
F06065	15.8	1.051	77.3	155.5 §	103.8	1.22	2.46	1.64
F06066	18.1	1.039	51.7	113.9	39.1	0.94	2.06	0.71
F06067	12.1	1.055	65.2	165.4 §	83.6	0.79	2.00	1.01
Number of females	5	5	5	5	5	5	5	5
Mean	14.5 *	1.041 *	59.5 **	123.8 *	54.1 *	0.86	1.79	0.78
±S.D.	2.7	0.012	11.6	34.8	37.6	0.24	0.57	0.57

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.
Significantly different from the control group (*: P<0.05, **: P<0.01).
Turbidity, -: negative +: slight
Protein, -: negative; ±: 10≦and＜30 mg/dL; +: 30≦and＜100 mg/dL
Glucose, -: negative
Ketone, -: negative; ±: 5≦and＜10 mg/dL; +: 10≦and＜40 mg/dL
Bilirubin, -: negative
Occult blood, -: negative
Urobilinogen, ±: normal; +: 2.0≦and＜4.0 mg/dL
Red blood cells, White blood cells and Casts, -: not observed
Crystals and Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 24-2-1. Urinalysis in female rats of the recovery period

Control (vehicle: water for injection)

Female No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells[a)]	White blood cells[a)]	Casts[a)]	Crystals[b)]	Epithelial cells[b)]
F05054	Light yellow	-	6.5	+	-	+	-	-	2+	-	-	-	±	-
F05055	Light yellow	-	7.5	-	-	-	-	-	±	-	-	-	-	-
F05056	Light yellow	-	7.0	+	-	+	-	-	+	-	-	-	±	-
F05057	Light yellow	-	6.5	+	-	±	-	-	±	-	-	-	-	-
F05058	Light yellow	-	6.5	-	-	-	-	-	±	-	-	-	-	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F05054	10.3	1.068	144.8	240.2 §	148.0	1.49	2.47	1.52
F05055	20.6	1.040	69.0	154.4	89.2	1.42	3.18	1.84
F05056	6.5	1.053	87.4	143.6 §	78.2	0.57	0.93	0.51
F05057	7.2	1.079	135.9	252.7 §	181.0	0.98	1.82	1.30
F05058	11.6	1.039	76.6	174.0 §	92.6	0.89	2.02	1.07
Number of females	5	5	5	5	5	5	5	5
Mean	11.2	1.056	102.7	193.0	117.8	1.07	2.08	1.25
±S.D.	5.6	0.018	35.1	50.2	44.5	0.38	0.83	0.50

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.
Turbidity, -: negative
Protein, -: negative; ±: 10≦and＜30 mg/dL; +: 30≦and＜100 mg/dL; 2+: 100≦and＜300 mg/dL
Glucose, -: negative
Ketone, -: negative; ±: 5≦and＜10 mg/dL; +: 10≦and＜40 mg/dL
Bilirubin, -: negative
Occult blood, -: negative
Urobilinogen, ±: normal; +: 2.0≦and＜4.0 mg/dL
Red blood cells, White blood cells and Casts, -: not observed
Crystals and Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 24-2-2. Urinalysis in female rats of the recovery period

SF (150/75 mg/kg)

Female No.	Quality									Urinary sediments				
	Color	Turbidity	pH	Protein	Glucose	Ketone	Bilirubin	Occult blood	Urobilinogen	Red blood cells[a)]	White blood cells[a)]	Casts[a)]	Crystals[b)]	Epithelial cells[b)]
F06066	Light yellow	-	6.5	+	-	±	-	-	+	-	-	-	-	-
F06067	Light yellow	-	6.5	+	-	±	-	-	+	-	-	-	±	-
F06068	Light yellow	-	7.0	-	-	-	-	-	±	-	-	-	±	-

Female No.	Urine volume (mL/24hr)	Specific gravity	Electrolyte, density (mEq/L)			Electrolyte, gross volume (mEq/24 hr)		
			Na	K	Cl	Na	K	Cl
F06066	5.8	1.066	81.6	169.8	51.7	0.47	0.98	0.30
F06067	8.1	1.064	115.0	220.1	123.8	0.93	1.78	1.00
F06068	14.3	1.036	71.6	111.3 §	77.3	1.02	1.59	1.11
Number of females	5	5	5	5	5	5	5	5
Mean	13.3	1.050	90.2	172.9	89.6	1.16	2.23	1.22
±S.D.	6.4	0.015	20.1	43.8	27.5	0.53	1.11	0.65

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were employed as the data.
Significantly different from the control group (*: P<0.05, **: P<0.01).
Turbidity, -: negative
Protein, -: negative; ±: 10≦and＜30 mg/dL; +: 30≦and＜100 mg/dL; 2+: 100≦and＜300 mg/dL
Glucose, -: negative
Ketone, -: negative; ±: 5≦and＜10 mg/dL; +: 10≦and＜40 mg/dL
Bilirubin, -: negative
Occult blood, -: negative
Urobilinogen, ±: normal; +: 2.0≦and＜4.0 mg/dL
Red blood cells, White blood cells and Casts, -: not observed
Crystals and Epithelial cells, -: not observed; ±: a few

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 25-1-1. Hematological findings of male rats at the end of the dosing period

Control (vehicle: water for injection)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
M01001	790	14.6	41.5	52.5	18.5	35.2	104.1	17.4	25.8
M01002	812	14.9	41.2	50.7	18.3	36.2	103.0	15.1	23.5
M01003	805	15.4	43.2	53.7	19.1	35.6	115.9	14.3	24.5
M01004	855	15.7	44.5	52.0	18.4	35.3	130.1	25.4	29.7
M01005	902	16.0	45.4	50.3	17.7	35.2	117.1	28.3	30.3
Number of males	5	5	5	5	5	5	5	5	5
Mean	833	15.3	43.2	51.8	18.4	35.5	114.0	20.1	26.8
S.D.	46	0.6	1.8	1.4	0.5	0.4	11.1	6.3	3.1

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
M01001	61.1	20.3	1.5	0.0	4.7	73.5	3.33
M01002	81.9	24.1	2.7	0.0	6.5	66.7	4.60
M01003	69.6	25.9	2.0	0.0	3.3	68.8	2.67
M01004	58.7	19.8	2.0	0.0	5.5	72.7	2.65
M01005	104.9	22.0	1.5	0.0	3.5	73.0	2.95
Number of males	5	5	5	5	5	5	5
Mean	75.2	22.4	1.9	0.0	4.7	70.9	3.24
S.D.	18.9	2.6	0.5	0.0	1.3	3.0	0.81

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 25-1-2. Hematological findings of male rats at the end of the dosing period

SF (15 mg/kg)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
M02013	863	15.8	43.5	50.4	18.3	36.3	98.5	22.3	27.4
M02014	932	16.7	46.4	49.8	17.9	36.0	117.9	24.0	27.4
M02015	791	14.5	42.1	53.2	18.3	34.4	99.1	17.5 §	28.0
M02016	801	14.5	42.7	53.3	18.1	34.0	99.3	21.3	28.2
M02017	811	14.4	40.8	50.3	17.8	35.3	122.6	17.1	25.4
Number of males	5	5	5	5	5	5	5	5	5
Mean	840	15.2	43.1	51.4	18.1	35.2	107.5	20.4	27.3
S.D.	59	1.0	2.1	1.7	0.2	1.0	11.8	3.0	1.1

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
M02013	75.6	12.8	1.5	0.1	2.1	83.5	2.28
M02014	63.4	13.4	1.4	0.0	3.3	81.9	2.83
M02015	65.5	39.1	1.2	0.0	3.7	56.0	2.54
M02016	45.1	26.4	1.1	0.0	4.7	67.8	3.00
M02017	60.7	31.5	2.3	0.0	3.6	62.6	3.94
Number of males	5	5	5	5	5	5	5
Mean	62.1	24.6	1.5	0.0	3.5	70.4	2.92
S.D.	11.0	11.5	0.5	0.0	0.9	12.0	0.63

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit.
The re-measured values were employed as the data.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 25-1-3. Hematological findings of male rats at the end of the dosing period

SF (50 mg/kg)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
M03025	801	15.2	43.4	54.2	19.0	35.0	94.5	19.1 §	30.5
M03026	858	15.2	42.0	49.0	17.7	36.2	123.0	22.9	25.5
M03027	775	15.6	46.8	60.4	20.1	33.3	104.3	17.6	26.2
M03028	811	14.9	42.4	52.3	18.4	35.1	108.4	23.7	29.7
M03029	825	15.7	44.8	54.3	19.0	35.0	98.6	23.0	28.7
Number of males	5	5	5	5	5	5	5	5	5
Mean	814	15.3	43.9	54.0	18.8	34.9	105.8	21.3	28.1
S.D.	31	0.3	2.0	4.2	0.9	1.0	11.0	2.7	2.2

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
M03025	104.4	11.6	1.7	0.0	3.4	83.3	2.95
M03026	71.8	20.2	1.7	0.0	5.4	72.7	2.51
M03027	64.7	19.3	1.7	0.0	4.0	75.0	3.19
M03028	65.8	23.2	1.8	0.0	3.3	71.7	3.86
M03029	59.0	31.4	1.0	0.0	2.0	65.6	2.96
Number of males	5	5	5	5	5	5	5
Mean	73.1	21.1	1.6	0.0	3.6	73.7	3.09
S.D.	18.1	7.2	0.3	0.0	1.2	6.4	0.49

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit.
The re-measured values were employed as the data.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 25-1-4. Hematological findings of male rats at the end of the dosing period

SF (150/75 mg/kg)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
M04037	795	14.6	41.3	51.9	18.4	35.4	120.3	17.3	25.6
M04038	791	15.0	43.0	54.4	19.0	34.9	129.1	15.9	20.5
M04039	828	15.2	44.7	54.0	18.4	34.0	110.7	24.5	30.0 §
M04040	892	15.9	45.1	50.6	17.8	35.3	136.3	22.4	27.6
M04041	773	14.5	42.2	54.6	18.8	34.4	111.0	14.3	24.2
Number of males	5	5	5	5	5	5	5	5	5
Mean	816	15.0	43.3	53.1	18.5	34.8	121.5	18.9	25.6
S.D.	47	0.6	1.6	1.8	0.5	0.6	11.2	4.4	3.6

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
M04037	130.1	7.6	1.3	0.0	3.3	87.8	2.41
M04038	120.7	25.3	1.3	0.0	3.1	70.3	4.81
M04039	69.2	21.9	2.3	0.0	4.0	71.8	4.11
M04040	71.4	21.2	2.2	0.0	4.6	72.0	2.94
M04041	88.5	28.2	1.9	0.1	3.1	66.7	2.72
Number of males	5	5	5	5	5	5	5
Mean	96.0	20.8	1.8	0.0	3.6	73.7	3.40
S.D.	28.1	7.9	0.5	0.0	0.7	8.2	1.02

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit.
The re-measured values were employed as the data.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 25-2-1. Hematological findings of male rats at the end of the recovery period

Control (vehicle: water for injection)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
M01008	730	13.6	39.0	53.4	18.6	34.9	89.3	12.7	20.7
M01009	779	14.5	41.5	53.3	18.6	34.9	87.8	17.7	25.1
M01010	787	14.1	41.9	53.2	17.9	33.7	121.2	15.7	25.2 §
M01011	768	13.9	40.5	52.7	18.1	34.3	69.0	16.0	22.7
M01012	812	13.9	41.6	51.2	17.1	33.4	96.6	18.9	29.2
Number of males	5	5	5	5	5	5	5	5	5
Mean	775	14.0	40.9	52.8	18.1	34.2	92.8	16.2	24.6
S.D.	30	0.3	1.2	0.9	0.6	0.7	18.9	2.3	3.2

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
M01008	97.1	15.8	2.0	0.0	3.6	78.6	4.96
M01009	105.1	18.4	1.5	0.1	4.2	75.8	3.30
M01010	122.2	12.3	1.5	0.1	3.6	82.5	3.93
M01011	97.9	11.2	2.2	0.0	3.5	83.1	3.43
M01012	55.8	14.9	2.3	0.0	4.5	78.3	2.42
Number of males	5	5	5	5	5	5	5
Mean	95.6	14.5	1.9	0.0	3.9	79.7	3.61
S.D.	24.4	2.9	0.4	0.1	0.4	3.1	0.93

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit.
The re-measured values were employed as the data.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 25-2-2. Hematological findings of male rats at the end of the recovery period

SF (150/75 mg/kg)

Male No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
M04043	772	14.1	42.6	55.2	18.3	33.1	107.5	17.6	28.9
M04044	785	14.3	43.7	55.7	18.2	32.7	84.3	25.1	31.3 §
M04045	784	14.2	42.5	54.2	18.1	33.4	102.0	17.7	27.6
M04047	767	14.6	44.0	57.4	19.0	33.2	86.5	19.9	27.9
M04048	804	14.2	42.8	53.2	17.7	33.2	106.3	14.6	23.7
Number of males	5	5	5	5	5	5	5	5	5
Mean	782	14.3	43.1 **	55.1 *	18.3	33.1 *	97.3	19.0	27.9
S.D.	14	0.2	0.7	1.6	0.5	0.3	11.1	3.9	2.8

Male No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
M04043	92.1	6.8	1.1	0.0	3.4	88.7	2.43
M04044	73.0	14.0	1.4	0.1	3.3	81.2	2.74
M04045	72.6	17.0	1.4	0.0	3.4	78.2	2.71
M04047	68.5	25.8	2.2	0.0	4.7	67.3	2.13
M04048	72.0	16.6	1.3	0.0	2.4	79.7	3.11
Number of males	5	5	5	5	5	5	5
Mean	75.6	16.0	1.5	0.0	3.4	79.0	2.62
S.D.	9.4	6.8	0.4	0.0	0.8	7.7	0.37

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit.
The re-measured values were employed as the data.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 26-1-1. Hematological findings of female rats at the end of the dosing period

Control (vehicle: water for injection)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
F01003	697	13.9	41.5	59.5	19.9	33.5	120.6	13.1	22.1
F01004	677	13.3	40.2	59.4	19.6	33.1	114.7	12.9	22.0
F01005	694	14.2	42.1	60.7	20.5	33.7	121.5	12.9	18.1
F01006	506	11.1	34.9	69.0	21.9	31.8	165.3	12.4	20.0
F01010	712	14.7	43.1	60.5	20.6	34.1	118.9	12.5	18.6
Number of females	5	5	5	5	5	5	5	5	5
Mean	657	13.4	40.4	61.8	20.5	33.2	128.2	12.8	20.2
S.D.	85	1.4	3.2	4.1	0.9	0.9	20.9	0.3	1.9

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
F01003	86.4	34.6	1.3	0.0	4.3	59.8	10.53
F01004	118.9	26.6	0.4	0.0	3.6	69.4	8.88
F01005	90.6	23.3	0.8	0.0	4.4	71.5	7.49
F01006	73.7	11.6	0.1	0.0	3.4	84.9	20.61
F01010	66.0	27.0	0.9	0.0	3.8	68.3	7.90
Number of females	5	5	5	5	5	5	5
Mean	87.1	24.6	0.7	0.0	3.9	70.8	11.08
S.D.	20.3	8.4	0.5	0.0	0.4	9.1	5.45

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 26-1-2. Hematological findings of female rats at the end of the dosing period

SF (15 mg/kg)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
F02013	730	13.4	40.1	54.9	18.4	33.4	107.7	13.0	18.8
F02014	680	13.8	40.9	60.1	20.3	33.7	121.6	12.4	20.6
F02015	759	14.5	42.8	56.4	19.1	33.9	97.2	11.7	18.2
F02016	643	13.0	39.4	61.3	20.2	33.0	128.7	12.5	18.2
F02017	684	12.4	38.5	56.3	18.1	32.2	104.0	13.4	19.9
Number of females	5	5	5	5	5	5	5	5	5
Mean	699	13.4	40.3	57.8	19.2	33.2	111.8	12.6	19.1
S.D.	46	0.8	1.6	2.7	1.0	0.7	13.0	0.6	1.1

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
F02013	71.4	29.7	1.8	0.0	5.9	62.6	5.45
F02014	83.3	18.2	0.8	0.1	3.1	77.8	7.53
F02015	146.4	34.3	0.8	0.1	4.0	60.8	7.39
F02016	123.3	13.2	0.4	0.0	3.4	83.0	7.59
F02017	91.2	31.5	1.2	0.0	3.8	63.5	6.83
Number of females	5	5	5	5	5	5	5
Mean	103.1	25.4	1.0	0.0	4.0	69.5	6.96
S.D.	30.9	9.2	0.5	0.1	1.1	10.1	0.89

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 26-1-3. Hematological findings of female rats at the end of the dosing period

SF (50 mg/kg)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
F03025	650	12.3	37.3	57.4	18.9	33.0	164.7	13.1	20.6
F03026	652	13.3	39.9	61.2	20.4	33.3	130.6	12.8	20.2
F03030	709	13.7	41.5	58.5	19.3	33.0	98.4	12.9	19.0
F03033	712	13.8	41.1	57.7	19.4	33.6	99.0	13.0	20.5
F03036	660	13.5	41.3	62.6	20.5	32.7	124.1	12.5	21.6 §
Number of females	5	5	5	5	5	5	5	5	5
Mean	677	13.3	40.2	59.5	19.7	33.1	123.4	12.9	20.4
S.D.	31	0.6	1.7	2.3	0.7	0.3	27.3	0.2	0.9

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
F03025	144.6	17.9	0.9	0.0	3.0	78.2	7.71
F03026	87.0	34.3	1.0	0.0	3.8	60.9	6.87
F03030	51.9	17.2	1.7	0.0	5.0	76.1	6.75
F03033	71.5	14.9	0.6	0.0	3.4	81.1	4.78
F03036	58.5	47.4	0.5	0.0	4.6	47.5	10.63
Number of females	5	5	5	5	5	5	5
Mean	82.7	26.3	0.9	0.0	4.0	68.8	7.35
S.D.	37.1	14.1	0.5	0.0	0.8	14.2	2.13

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit.
The re-measured values were employed as the data.
Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 26-1-4. Hematological findings of female rats at the end of the dosing period

SF (150/75 mg/kg)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times10^4/\mu L$)	(sec)	(sec)
F04037	612	11.9	37.0	60.5	19.4	32.2	108.4	11.8	20.1
F04038	669	12.8	38.0	56.8	19.1	33.7	121.8	12.5	19.2
F04041	776	14.3	42.7	55.0	18.4	33.5	123.5	11.2	17.8
F04042	672	13.4	40.8	60.7	19.9	32.8	107.8	12.8	21.4
F04047	708	13.6	40.8	57.6	19.2	33.3	117.1	12.5	21.0
Number of females	5	5	5	5	5	5	5	5	5
Mean	687	13.2	39.9	58.1	19.2	33.1	115.7	12.2	19.9
S.D.	60	0.9	2.3	2.5	0.5	0.6	7.3	0.7	1.4

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
F04037	117.4	51.9	1.7	0.0	3.7	42.7	7.54
F04038	76.3	13.3	1.0	0.0	4.2	81.5	6.25
F04041	110.2	38.4	1.2	0.1	4.8	55.5	5.39
F04042	103.0	46.9	1.7	0.0	4.1	47.3	5.52
F04047	56.4	20.6	0.9	0.0	3.0	75.5	8.05
Number of females	5	5	5	5	5	5	5
Mean	92.7	34.2	1.3	0.0	4.0	60.5	6.55
S.D.	25.5	16.7	0.4	0.0	0.7	17.2	1.20

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 26-2-1. Hematological findings of female rats at the end of the dosing period, satellite group

Control (vehicle: water for injection)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
F05049	816	15.4	43.5	53.3	18.9	35.4	101.8	11.1	18.4
F05050	775	14.7	41.0	52.9	19.0	35.9	112.2	11.5	20.7
F05051	767	14.5	40.3	52.5	18.9	36.0	119.1	11.6	19.7
F05052	766	14.4	41.6	54.3	18.8	34.6	105.4	11.1	18.7
F05053	799	14.9	42.5	53.2	18.6	35.1	91.2	12.0	17.9
Number of females	5	5	5	5	5	5	5	5	5
Mean	785	14.8	41.8	53.2	18.8	35.4	105.9	11.5	19.1
S.D.	22	0.4	1.3	0.7	0.2	0.6	10.6	0.4	1.1

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
F05049	74.7	10.4	1.9	0.0	1.9	85.8	3.48
F05050	115.7	9.9	0.8	0.0	2.4	86.9	3.07
F05051	66.6	11.7	0.9	0.0	3.0	84.4	2.25
F05052	57.6	19.1	1.0	0.0	2.1	77.8	3.25
F05053	42.3	10.6	1.9	0.0	2.4	85.1	3.08
Number of females	5	5	5	5	5	5	5
Mean	71.4	12.3	1.3	0.0	2.4	84.0	3.03
S.D.	27.5	3.8	0.6	0.0	0.4	3.6	0.46

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 26-2-2. Hematological findings of female rats at the end of the dosing period, satellite group

SF (150/75 mg/kg)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
F06059	801	15.2	43.2	53.9	19.0	35.2	99.5	11.6	16.9
F06064	706	13.5	38.9	55.1	19.1	34.7	102.1	11.4	17.5
F06065	770	14.9	42.2	54.8	19.4	35.3	142.8	12.1	23.0
Number of females	3	3	3	3	3	3	3	3	3
Mean	759	14.5	41.4	54.6 *	19.2 *	35.1	114.8	11.7	19.1
S.D.	48	0.9	2.3	0.6	0.2	0.3	24.3	0.4	3.4

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
F06059	55.0	7.2	2.4	0.0	2.4	88.0	3.14
F06064	81.4	4.6	1.7	0.0	1.6	92.1	2.63
F06065	69.6	9.0	1.7	0.1	3.4	85.8	3.00
Number of females	3	3	3	3	3	3	3
Mean	68.7	6.9	1.9	0.0	2.5	88.6	2.92
S.D.	13.2	2.2	0.4	0.1	0.9	3.2	0.26

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 26-3-1. Hematological findings of female rats at the end of the recovery period

Control (vehicle: water for injectio)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
F05054	819	15.2	44.8	54.7	18.6	33.9	97.4	12.1	25.8
F05055	787	14.6	42.1	53.5	18.6	34.7	89.0	12.1	21.0
F05056	769	14.3	43.3	56.3	18.6	33.0	93.3	12.3	23.4
F05057	668	12.8	38.4	57.5	19.2	33.3	89.0	12.4	20.9
F05058	691	12.9	38.4	55.6	18.7	33.6	80.5	11.6	22.0
Number of females	5	5	5	5	5	5	5	5	5
Mean	747	14.0	41.4	55.5	18.7	33.7	89.8	12.1	22.6
S.D.	65	1.1	2.9	1.5	0.3	0.7	6.3	0.3	2.0

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
F05054	39.4	20.3	3.8	0.0	5.6	70.3	3.64
F05055	53.3	20.4	2.3	0.0	3.6	73.7	3.17
F05056	42.9	9.1	2.3	0.0	2.8	85.8	2.40
F05057	30.4	17.2	2.3	0.0	3.9	76.6	2.83
F05058	25.3	23.7	2.8	0.0	5.1	68.4	3.11
Number of females	5	5	5	5	5	5	5
Mean	38.3	18.1	2.7	0.0	4.2	75.0	3.03
S.D.	10.9	5.6	0.7	0.0	1.1	6.8	0.46

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 26-3-2. Hematological findings of female rats at the end of the recovery period

SF (150/75 mg/kg)

Female No.	RBC	HGB	HCT	MCV	MCH	MCHC	PLT	PT	APTT
	($\times 10^4/\mu L$)	(g/dL)	(%)	(fL)	(pg)	(g/dL)	($\times 10^4/\mu L$)	(sec)	(sec)
F06066	690	13.5	41.3	59.9	19.6	32.7	68.8	11.7	19.6
F06067	875	16.2	43.6	49.8	18.5	37.2	#	11.6	19.1
F06068	675	12.4	38.2	56.6	18.4	32.5	68.8	12.3	18.6
Number of females	3	3	3	3	3	3	2	3	3
Mean	747	14.0	41.0	55.4	18.8	34.1	68.8	11.9	19.1 *
S.D.	111	2.0	2.7	5.2	0.7	2.7	0.0	0.4	0.5

Female No.	WBC	NEUT	EOSI	BASO	MONO	LYMPH	RET
	($\times 10^2/\mu L$)	(%)	(%)	(%)	(%)	(%)	(%)
F06066	51.3	16.0	2.3	0.0	3.7	78.0	2.33
F06067	51.8	15.4	2.9	0.0	2.5	79.2	2.08
F06068	42.0	19.8	1.2	0.0	3.8	75.2	2.72
Number of females	3	3	3	3	3	3	3
Mean	48.4	17.1	2.1	0.0	3.3	77.5	2.38
S.D.	5.5	2.4	0.9	0.0	0.7	2.1	0.32

The data was not avaiavle because the first and second measurements were out of the control value

Significantly different from the control group (*: P<0.05, **: P<0.01).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 27-1-1. Biochemical findings of male rats at the end of the dosing period

Control (vehicle: water for injection)

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M01001	5.8	3.6	1.64	140	30	22	61	65	32	0	163	15.6	18	0.6	0.05	316
M01002	5.7	3.5	1.59	126	49	29	83	72	33	0	344	9.7	17	0.5	0.05	380
M01003	5.3	3.4	1.79	128	51	26	86	53	26	0	66	5.5	18	0.4	0.05	235
M01004	5.6	3.7	1.95	130	57	30	91	57	25	0	306	13.5	20	0.5	0.05	386
M01005	5.8	3.6	1.64	133	49	23	76	61	25	0	65	7.0	19	0.6	0.05	293
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.6	3.6	1.72	131	47	26	79	62	28	0	189	10.3	18	0.5	0.05	322
S.D.	0.2	0.1	0.15	5	10	4	12	7	4	0	131	4.3	1	0.1	0	63

Control (vehicle: water for injection)

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M01001	6.4	9.3	142.1	4.32	105.9
M01002	6.0	9.4	144.2	3.97	108.4
M01003	6.1	9.2	143.2	4.20	107.4
M01004	5.9	9.7	143.4	4.18	107.9
M01005	5.8	9.7	143.9	3.71	107.3
Number of males	5	5	5	5	5
Mean	6.0	9.5	143.4	4.08	107.4
S.D.	0.2	0.2	0.8	0.24	0.9

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 27-1-2. Biochemical findings of male rats at the end of the dosing period

SF 15 mg/kg

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M02013	5.3	3.4	1.79	132	51	16	82	72	32	0	123	8.9	18	0.5	0.06	266
M02014	5.2	3.6	2.25	132	36	19	68	74	41	0	93	20.5	20	0.5	0.06	299
M02015	5.6	3.3	1.43	106	59	24	91	67	31	0	82	5.2	24	0.5	0.05	384
M02016	5.4	3.4	1.70	119	33	24	63	79	36	0	44	12.8	20	0.6	0.05	380
M02017	5.3	3.4	1.79	118	46	32	80	69	30	0	60	9.3	16	0.5	0.05	294
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.4	3.4	1.79	121	45	23	77	72	34	0	80	11.3	20	0.5	0.05	325
S.D.	0.2	0.1	0.30	11	11	6	11	5	5	0	30	5.8	3	0	0.01	54
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN	AN	KW	AN	AN	AN	AN	KW	AN	AN	AN	AN	AN

SF 15 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M02013	5.0	8.8	144.2	3.73	109.7
M02014	6.2	9.2	144.0	4.13	107.7
M02015	6.0	9.1	143.7	3.71	107.1
M02016	6.5	9.3	143.2	4.29	106.6
M02017	5.3	9.2	143.9	3.91	108.1
Number of males	5	5	5	5	5
Mean	5.8	9.1	143.8	3.95	107.8
S.D.	0.6	0.2	0.4	0.25	1.2
Significance	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 27-1-3. Biochemical findings of male rats at the end of the dosing period

SF 50 mg/kg

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M03025	5.3	3.5	1.94	124	74	20	101	90	50	0	114	12.9	16	0.6	0.11	511
M03026	5.2	3.4	1.89	121	39	18	67	69	28	0	175	16	19	0.5	0.06	297
M03027	5.0	3.5	2.33	141	52	59	96	56	23	0	93	6.6	17	0.4	0.06	359
M03028	5.0	3.3	1.94	111	41	38	74	67	31	0	54	5.6	19	0.4	0.07	328
M03029	5.3	3.5	1.94	121	37	17	67	72	29	0	181	4.8	18	0.5	0.05	434
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.2	3.4	2.01	124	49	30	81	71	32	0	123	9.2	18	0.5	0.07	386
S.D.	0.2	0.1	0.18	11	15	18	16	12	10	0	54	5.0	1	0.1	0.02	87
Significance	**	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN	AN	KW	AN	AN	AN	AN	KW	AN	AN	AN	AN	AN

SF 50 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M03025	7.7	9.2	143.4	4.38	106.0
M03026	5.5	9.1	143.3	4.27	106.9
M03027	7.6	8.7	144.2	4.13	109.4
M03028	6.2	9.4	144.0	3.83	107.2
M03029	5.7	9.3	144.6	3.62	107.5
Number of males	5	5	5	5	5
Mean	6.5	9.1	143.9	4.05	107.4
S.D.	1	0.3	0.5	0.32	1.3
Significance	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 27-1-4. Biochemical findings of male rats at the end of the dosing period

SF 150/75 mg/kg

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M04037	5.2	3.4	1.89	148	45	28	75	58	28	0	181	12.3	19	0.6	0.08	403
M04038	5.8	3.8	1.90	146	41	20	69	62	30	0	398	6.4	17	0.6	0.07	286
M04039	5.2	3.6	2.25	106	45	19	78	96	40	0	178	17.9	16	0.5	0.06	430
M04040	5.2	3.6	2.25	138	63	72	107	73	40	0	146	11.5	23	0.5	0.07	319
M04041	4.9	3.2	1.88	139	33	19	58	61	32	0	39	4.6	15	0.4	0.05	285
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.3	3.5	2.03	135	45	32	77	70	34	0	188	10.5	18	0.5	0.07	345
S.D.	0.3	0.2	0.20	17	11	23	18	16	6	0	131	5.3	3	0.1	0.01	68
Significance	*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	DU	AN	AN	AN	AN	KW	AN	AN	AN	AN	KW	AN	AN	AN	AN	AN

SF 150/75 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M04037	6.0	9.1	142.9	4.05	108.4
M04038	6.1	9.8	143.7	3.93	106.2
M04039	6.4	9.4	143.6	4.09	107.3
M04040	5.7	9.2	143.0	3.85	108.3
M04041	6.8	9.1	144.9	3.54	109.9
Number of males	5	5	5	5	5
Mean	6.2	9.3	143.6	3.89	108
S.D.	0.4	0.3	0.8	0.22	1.4
Significance	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.

DU: Analysis by Dunnett's test.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 27-2-1. Biochemical findings of male rats at the end of the recovery period

Control (vehicle: water for injection)

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M01008	5.5	3.6	1.89	133	59	16	87	85	37	0	270	27.1	15	0.6	0.08	277
M01009	5.3	3.6	2.12	125	38	21	66	74	39	0	109	10.0	15	0.5	0.07	301
M01010	5.9	3.8	1.81	143	87	46	120	52	24	0	67	13.0	15	0.5	0.06	212
M01011	5.6	3.6	1.80	151	72	17	94	72	27	0	195	58.3	15	0.6	0.08	271
M01012	5.4	3.6	2.00	138	48	15	78	64	28	0	74	11.7	14	0.5	0.05	384
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.5	3.6	1.92	138	61	23	89	69	31	0	143	24.0	15	0.5	0.07	289
S.D.	0.2	0.1	0.14	10	19	13	20	12	7	0	87	20.3	0	0.1	0.01	62

Control (vehicle: water for injection)

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M01008	6.8	9.1	143.2	3.58	106.0
M01009	6.4	9.3	141.7	3.93	106.2
M01010	5.7	9.8	143.0	3.54	105.2
M01011	5.3	9.2	143.6	3.90	106.0
M01012	4.9	9.2	143.6	3.50	108.6
Number of males	5	5	5	5	5
Mean	5.8	9.3	143	3.69	106.4
S.D.	0.8	0.3	0.8	0.21	1.3

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 27-2-2. Biochemical findings of male rats at the end of the recovery period

SF 150/75 mg/kg

Male No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
M04043	5.5	3.6	1.89	150	61	21	92	73	28	0	235	17.4	15	0.5	0.07	255
M04044	5.2	3.3	1.74	201	37	36	68	71	31	0	252	12.1	16	0.5	0.05	373
M04045	5.5	3.5	1.75	134	50	21	75	66	28	0	118	13.5	18	0.6	0.05	276
M04047	5.7	3.6	1.71	166	54	21	83	65	23	0	246	8.3	15	0.5	0.06	289
M04048	5.4	3.6	2.00	167	40	16	71	57	20	0	139	9.0	12	0.5	0.06	315
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.5	3.5	1.82	164	48	23	78	66	26	0	198	12.1	15	0.5	0.06	302
S.D.	0.2	0.1	0.12	25	10	8	10	6	4	0	64	3.7	2	0	0.01	45
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	AW	AW	TT	TT	TT

SF 150/75 mg/kg

Male No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
M04043	6.1	9.4	143.4	3.66	106.6
M04044	7.0	8.9	143.5	3.67	106.2
M04045	7.0	9.2	142.8	4.10	106.9
M04047	6.0	9.4	145.0	3.62	108.0
M04048	6.3	9.5	145.1	3.59	108.5
Number of males	5	5	5	5	5
Mean	6.5	9.3	144.0	3.73	107.2
S.D.	0.5	0.2	1.0	0.21	1.0
Significance	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.
AW: Analysis by Aspin-Welch t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 28-1-1. Biochemical findings of female rats at the end of the dosing period

Control (vehicle: water for injection)

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F01003	6.1	4.0	1.90	138	42	28	88	72	40	0	47	15.8	19	0.5	0.09	166
F01004	5.9	4.1	2.28	103	67	34	125	87	44	0	320	17.9	16	0.6	0.10	162
F01005	5.5	3.7	2.06	118	46	19	88	72	44	0	48	9.0	15	0.5	0.06	165
F01006	5.7	3.7	1.85	117	44	21	81	86	41	0	164	5.7	15	0.6	0.07	153
F01010	5.6	3.9	2.29	118	49	16	102	62	31	0	40	25.1	23	0.6	0.07	183
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.8	3.9	2.08	119	50	24	97	76	40	0	124	14.7	18	0.6	0.08	166
S.D.	0.2	0.2	0.21	12	10	7	18	11	5	0	121	7.6	3	0.1	0.02	11

Control (vehicle: water for injection)

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F01003	7.0	9.3	141.4	4.14	105.3
F01004	6.6	9.7	142.0	3.82	109.3
F01005	5.3	9.1	140.2	3.96	106.8
F01006	6.6	9.8	141.9	3.90	109.2
F01010	7.0	9.5	141.3	3.96	107.2
Number of females	5	5	5	5	5
Mean	6.5	9.5	141.4	3.96	107.6
S.D.	0.7	0.3	0.7	0.12	1.7

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 28-1-2. Biochemical findings of female rats at the end of the dosing period

SF 15 mg/kg

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F02013	5.4	3.7	2.18	117	32	14	70	83	35	0	43	17.9	16	0.5	0.07	163
F02014	6.1	4.2	2.21	123	65	16	116	80	37	0	182	7.9	19	0.7	0.05	134
F02015	5.7	3.9	2.17	131	49	65	110	78	41	0	52	20.9	16	0.5	0.10	166
F02016	5.5	3.9	2.44	113	34	17	73	105	45	0	86	15.0	20	0.5	0.07	134
F02017	5.8	3.9	2.05	118	39	19	84	102	49	0	152	10.0	17	0.6	0.05	380
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.7	3.9	2.21	120	44	26	91	90	41	0	103	14.3	18	0.6	0.07	195
S.D.	0.3	0.2	0.14	7	14	22	21	13	6	0	62	5.4	2	0.1	0.02	104
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	DU	AN	AN	AN	KW	AN	AN	AN	DT

SF 15 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F02013	6.6	9.3	140.6	3.59	107.5
F02014	6.2	10.0	139.0	4.22	104.9
F02015	7.2	9.3	140.1	3.64	104.8
F02016	6.6	9.4	140.1	3.46	106.8
F02017	7.2	9.4	142.9	3.58	109.4
Number of females	5	5	5	5	5
Mean	6.8	9.5	140.5	3.70	106.7
S.D.	0.4	0.3	1.4	0.30	1.9
Significance	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	KW	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).
DU: Analysis by Dunnett's test.
KW: Analysis by Kruskal-Wallis' test (one-way layout).
DT: Analysis by Dunnett type mean rank test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 28-1-3. Biochemical findings of female rats at the end of the dosing period

SF 50 mg/kg

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F03025	6.0	3.8	1.73	120	49	33	105	74	41	0	105	20.6	16	0.6	0.05	182
F03026	5.6	3.8	2.11	118	55	42	117	67	36	0	37	10.8	17	0.5	0.06	140
F03030	5.3	3.7	2.31	117	36	23	83	80	34	0	75	8.7	22	0.6	0.07	179
F03033	5.6	3.8	2.11	112	48	18	95	70	35	0	55	11.6	19	0.6	0.09	192
F03036	5.6	3.8	2.11	82	56	11	107	89	57	0	172	43.6	18	0.6	0.06	196
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.6	3.8	2.07	110	49	25	101	76	41	0	89	19.1	18	0.6	0.07	178
S.D.	0.2	0	0.21	16	8	12	13	9	10	0	53	14.5	2	0	0.02	22
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	DU	AN	AN	AN	KW	AN	AN	AN	DT

SF 50 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F03025	7.2	9.4	140.9	4.05	106.1
F03026	6.2	9.5	140.3	4.11	107.7
F03030	7.4	9.4	141.7	3.55	108.6
F03033	6.6	9.1	140.9	3.88	107.2
F03036	9.0	9.9	141.8	5.74	107.4
Number of females	5	5	5	5	5
Mean	7.3	9.5	141.1	4.27	107.4
S.D.	1.1	0.3	0.6	0.85	0.9
Significance	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	KW	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).
DU: Analysis by Dunnett's test.
KW: Analysis by Kruskal-Wallis' test (one-way layout).
DT: Analysis by Dunnett type mean rank test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 28-1-4. Biochemical findings of female rats at the end of the dosing period

SF 150/75 mg/kg

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F04037	6.1	4.2	2.21	116	78	27	142	140	52	0	302	15.1	19	0.7	0.07	217
F04038	5.5	3.7	2.06	111	46	24	95	73	30	0	103	15.9	22	0.6	0.07	266
F04041	5.9	4.2	2.47	126	53	28	116	78	38	0	54	13.1	20	0.6	0.06	285
F04042	6.2	4.2	2.10	99	50	16	110	111	48	0	186	17.4	22	0.7	0.06	243
F04047	5.7	3.9	2.17	120	46	17	94	124	57	0	71	9.2	14	0.5	0.07	199
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.9	4.0	2.20	114	55	22	111	105	45	0	143	14.1	19	0.6	0.07	242
S.D.	0.3	0.2	0.16	10	13	6	20	29	11	0	102	3.2	3	0.1	0.01	35
Significance	NS	NS	NS	NS	NS	NS	NS	*	NS	NS	NS	NS	NS	NS	NS	*
Statistical method	AN	AN	AN	AN	AN	AN	AN	DU	AN	AN	AN	KW	AN	AN	AN	DT

SF 150/75 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F04037	6.3	9.7	139.6	3.94	106.8
F04038	7.8	9.5	142.0	4.08	108.3
F04041	7.5	9.7	142.0	3.68	107.8
F04042	9.5	10.0	144.4	3.46	108.6
F04047	6.3	9.6	142.8	3.41	108.1
Number of females	5	5	5	5	5
Mean	7.5	9.7	142.2	3.71	107.9
S.D.	1.3	0.2	1.7	0.29	0.7
Significance	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	KW	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).
DU: Analysis by Dunnett's test.
KW: Analysis by Kruskal-Wallis' test (one-way layout).
DT: Analysis by Dunnett type mean rank test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 28-2-1. Biochemical findings of female rats at the end of the dosing period, satellite group

Control (vehicle: water for injection)

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F05049	5.7	3.8	2.00	102	60	11	101	69	19	0	64	8.0	19	0.7	0.07	176
F05050	6.6	4.5	2.14	132	70	15	130	106	57	0	107	22.2	24	0.7	0.09	190
F05051	6.7	4.8	2.53	104	62	12	130	71	28	0	189	18.8	18	0.7	0.11	114
F05052	6.6	4.7	2.47	149	78	30	143	60	22	0	100	15.5	17	0.7	0.08	135
F05053	6.1	4.0	1.90	116	62	7	109	72	21	0	114	17.7	17	0.7	0.11	160
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	6.3	4.4	2.21	121	66	15	123	76	29	0	115	16.4	19	0.7	0.09	155
S.D.	0.4	0.4	0.28	20	8	9	17	18	16	0	46	5.3	3	0	0.02	31

Control (vehicle: water for injection)

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F05049	5.5	9.0	142.8	3.74	108.4
F05050	6.2	9.9	141.3	3.82	106.1
F05051	5.0	9.9	142.6	4.02	106.2
F05052	4.3	9.6	141.9	3.51	106.5
F05053	4.7	9.5	143.7	4.45	107.5
Number of females	5	5	5	5	5
Mean	5.1	9.6	142.5	3.91	106.9
S.D.	0.7	0.4	0.9	0.35	1.0

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 28-2-2. Biochemical findings of female rats at the end of the dosing period, satellite group

SF 150/75 mg/kg

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F06059	5.4	3.7	2.18	117	74	15	126	73	29	0	106	9.6	16	0.7	0.09	178
F06064	5.5	3.7	2.06	160	85	26	141	68	26	0	79	9.2	18	0.7	0.08	248
F06065	6.7	4.5	2.05	100	83	7	147	92	30	0	529	11.3	16	0.6	0.07	230
Number of females	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Mean	5.9	4.0	2.10	126	81	16	138	78	28	0	238	10.0	17	0.7	0.08	219
S.D.	0.7	0.5	0.07	31	6	10	11	13	2	0	252	1.1	1	0.1	0.01	36
Significance	NS	NS	NS	NS	*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	AW	TT	AW	TT	TT	TT	TT	TT

SF 150/75 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F06059	5.4	9.3	142.9	3.47	108.0
F06064	5.0	8.9	141.7	4.07	105.3
F06065	8.5	10.6	141.8	9.36 §	104.0
Number of females	3	3	3	3	3
Mean	6.3	9.6	142.1	5.63	105.8
S.D.	1.9	0.9	0.7	3.24	2.0
Significance	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	AW	TT

§, The re-measurement was carried out because the difference between two measured values exceeded the permissible limit. The re-measured values were

Significantly different from the control group (*: P<0.05, **: P<0.01).

NS: Not significantly different from the control group.

TT: Analysis by Student's t-test.

AW: Analysis by Aspin-Welch t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 28-3-1. Biochemical findings of female rats at the end of the recovery period

Control (vehicle: water for injection)

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F05054	5.9	4.1	2.28	126	64	12	113	55	19	0	96	10.5	16	0.6	0.06	141
F05055	6.1	4.3	2.39	135	60	27	116	60	19	0	63	10.9	13	0.6	0.08	160
F05056	5.9	4.1	2.28	140	61	17	109	51	17	0	80	5.8	14	0.8	0.06	102
F05057	5.1	3.6	2.40	134	48	9	92	73	34	0	55	9.2	17	0.6	0.08	211
F05058	5.9	4.0	2.11	128	65	9	120	60	24	0	47	9.9	18	0.8	0.06	139
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	5.8	4.0	2.29	133	60	15	110	60	23	0	68	9.3	16	0.7	0.07	151
S.D.	0.4	0.3	0.12	6	7	8	11	8	7	0	20	2.0	2	0.1	0.01	40

Control (vehicle: water for injection)

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F05054	4.9	9.5	141.8	3.80	107.5
F05055	3.6	9.4	143.1	3.27	107.1
F05056	3.6	8.9	143.2	3.43	106.6
F05057	4.2	8.5	143.8	4.26	108.9
F05058	3.9	9	142.7	3.42	104.4
Number of females	5	5	5	5	5
Mean	4.0	9.1	142.9	3.64	106.9
S.D.	0.5	0.4	0.7	0.4	1.6

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 28-3-2. Biochemical findings of female rats at the end of the recovery period

SF 150/75 mg/kg

Female No.	Total protein g/dL	Albumin g/dL	A/G	Glucose mg/dL	Total cholesterol mg/dL	Triglyceride mg/dL	Phospholipid mg/dL	AST U/L	ALT U/L	γ-GTP U/L	LDH U/L	Bile acid μmol/L	BUN mg/dL	Creatinine mg/dL	Total bilirubin mg/dL	ALP U/L
F06066	6.0	3.9	1.86	136	70	24	117	57	14	0	118	11.7	17	0.6	0.07	159
F06067	5.9	4.1	2.28	99	87	11	141	57	19	0	38	14.4	17	0.5	0.07	171
F06068	5.8	3.7	1.76	123	57	16	106	57	20	0	83	21.9	20	0.8	0.09	121
Number of females	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Mean	5.9	3.9	1.97	119	71	17	121	57	18	0	80	16.0	18	0.6	0.08	150
S.D.	0.1	0.2	0.28	19	15	7	18	0	3	0	40	5.3	2	0.2	0.01	26
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS	NS	NS
Statistical method	TT	TT	TT	AW	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

SF 150/75 mg/kg

Female No.	Inorganic phosphorus mg/dL	Ca mg/dL	Na mEq/L	K mEq/L	Cl mEq/L
F06066	4.8	9.1	144.4	3.52	108.9
F06067	4.2	8.9	143.1	3.67	110.0
F06068	5.9	9.6	143.9	3.68	106.7
Number of females	3	3	3	3	3
Mean	5	9.2	143.8	3.62	108.5
S.D.	0.9	0.4	0.7	0.09	1.7
Significance	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.
AW: Analysis by Aspin-Welch t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 29-1-1. Organ weights of male rats at the end of the dosing period

Control (vehicle: water for injection)

Male No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01001	440.6	1852.5	4.204	198.5	0.451	1439.5	3.267	11675.3	26.499	1562.2	3.546	1599.0	3.629	3161.2	7.175	704.3	1.599
M01002	506.3	2026.2	4.002	319.8	0.632	1378.1	2.722	12998.9	25.674	1621.2	3.202	1652.8	3.264	3274.0	6.467	871.3	1.721
M01003	400.2	1986.0	4.963	424.9	1.062	1150.5	2.875	10909.0	27.259	1534.9	3.835	1469.7	3.672	3004.6	7.508	648.7	1.621
M01004	470.4	2009.7	4.272	322.4	0.685	1484.2	3.155	12581.6	26.747	1611.9	3.427	1585.2	3.370	3197.1	6.797	653.9	1.390
M01005	487.5	1926.4	3.952	324.3	0.665	1312.7	2.693	12750.7	26.155	1453.8	2.982	1474.8	3.025	2928.6	6.007	843.5	1.730
M01006	436.4	1949.2	4.467	316.9	0.726	1295.7	2.969	12961.5	29.701	1545.7	3.542	1561.7	3.579	3107.4	7.121	904.7	2.073
M01007	432.0	2078.1	4.810	272.5	0.631	1320.5	3.057	11088.0	25.667	1637.4	3.790	1694.7	3.923	3332.1	7.713	801.1	1.854
Number of males	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Mean	453.3	1975.4	4.381	311.3	0.693	1340.2	2.963	12137.9	26.815	1566.7	3.475	1576.8	3.495	3143.6	6.970	775.4	1.713
S.D.	36.5	73.7	0.388	67.7	0.184	108.9	0.215	896.2	1.396	63.5	0.305	84.0	0.297	142.9	0.594	105.7	0.214

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 29-1-1(continued). Organ weights of male rats at the end of the dosing period

Control (vehicle: water for injection)

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides		Prostate, ventral		Seminal vesicles		Thyroid gland	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01001	1752.2	3.977	1757.2	3.988	3509.4	7.965	642.0	1.457	658.7	1.495	1300.7	2.952	518.2	1.176	1393.0	3.162	23.0	0.052
M01002	1787.7	3.531	1696.0	3.350	3483.7	6.881	821.2	1.622	648.0	1.280	1469.2	2.902	784.1	1.549	2216.9	4.379	23.4	0.046
M01003	1688.5	4.219	1750.1	4.373	3438.6	8.592	604.7	1.511	598.3	1.495	1203.0	3.006	638.8	1.596	1734.4	4.334	20.7	0.052
M01004	1518.6	3.228	1505.4	3.200	3024.0	6.429	618.4	1.315	620.7	1.320	1239.1	2.634	639.5	1.359	1465.4	3.115	15.3	0.033
M01005	1530.8	3.140	1537.1	3.153	3067.9	6.293	603.3	1.238	633.6	1.300	1236.9	2.537	783.5	1.607	1713.5	3.515	22.2	0.046
M01006	1720.6	3.943	1678.4	3.846	3399.0	7.789	723.9	1.659	669.6	1.534	1393.5	3.193	597.8	1.370	1607.8	3.684	21.9	0.050
M01007	1601.8	3.708	1590.8	3.682	3192.6	7.390	596.3	1.380	620.6	1.437	1216.9	2.817	550.7	1.275	1758.9	4.072	17.4	0.040
Number of males	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7	7
Mean	1657.2	3.678	1645.0	3.656	3302.2	7.334	658.5	1.455	635.6	1.409	1294.2	2.863	644.7	1.419	1698.6	3.752	20.6	0.046
S.D.	107.5	0.401	101.2	0.450	203.4	0.846	84.1	0.155	24.8	0.106	100.9	0.223	104.7	0.168	267.6	0.524	3.1	0.007

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 29-1-1(continued). Organ weights of male rats at the end of the dosing period

Control (vehicle: water for injection)

Male No.	Body weight (g)	Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01001	440.6	31.7	0.072	30.9	0.070	62.6	0.142
M01002	506.3	35.3	0.070	33.7	0.067	69.0	0.136
M01003	400.2	22.4	0.056	23.5	0.059	45.9	0.115
M01004	470.4	27.6	0.059	29.4	0.063	57.0	0.121
M01005	487.5	31.1	0.064	29.4	0.060	60.5	0.124
M01006	436.4	29.3	0.067	29.8	0.068	59.1	0.135
M01007	432.0	24.6	0.057	24.9	0.058	49.5	0.115
Number of males	7	7	7	7	7	7	7
Mean	453.3	28.9	0.064	28.8	0.064	57.7	0.127
S.D.	36.5	4.4	0.006	3.5	0.005	7.8	0.011

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 29-1-2. Organ weights of male rats at the end of the dosing period

SF 15 mg/kg

Male No.	Body weight (g)	Brain (mg)	Brain (mg/g)	Thymus (mg)	Thymus (mg/g)	Heart (mg)	Heart (mg/g)	Liver (mg)	Liver (mg/g)	Kidney (R) (mg)	Kidney (R) (mg/g)	Kidney (L) (mg)	Kidney (L) (mg/g)	Kidneys (mg)	Kidneys (mg/g)	Spleen (mg)	Spleen (mg/g)
M02013	400.7	1972.3	4.922	246.5	0.615	1293.4	3.228	9015.2	22.499	1446.7	3.610	1462.2	3.649	2908.9	7.260	689.2	1.720
M02014	412.9	1923.6	4.659	238.1	0.577	1381.3	3.345	9935.8	24.063	1370.0	3.318	1336.8	3.238	2706.8	6.556	734.1	1.778
M02015	481.5	2197.2	4.563	305.8	0.635	1456.6	3.025	12011.2	24.945	1604.8	3.333	1475.4	3.064	3080.2	6.397	669.6	1.391
M02016	471.0	2033.5	4.317	354.2	0.752	1532.7	3.254	11285.0	23.960	1430.8	3.038	1573.9	3.342	3004.7	6.379	935.9	1.987
M02017	493.7	2080.6	4.214	280.0	0.567	1360.6	2.756	12469.4	25.257	1389.6	2.815	1399.8	2.835	2789.4	5.650	785.0	1.590
M02018	476.1	1884.7	3.959	416.8	0.875	1466.6	3.080	12245.8	25.721	1547.9	3.251	1433.1	3.010	2981.0	6.261	802.4	1.685
M02019	432.9	1970.0	4.551	230.2	0.532	1268.9	2.931	9941.6	22.965	1265.6	2.924	1206.3	2.787	2471.9	5.710	588.9	1.360
M02020	444.8	1965.5	4.419	254.1	0.571	1318.4	2.964	11118.2	24.996	1502.6	3.378	1525.6	3.430	3028.2	6.808	842.8	1.895
M02021	391.0	1965.1	5.026	244.5	0.625	1100.2	2.814	10159.5	25.983	1571.6	4.019	1476.4	3.776	3048.0	7.795	609.7	1.559
M02022	457.7	1900.8	4.153	321.8	0.703	1367.1	2.987	11904.7	26.010	1613.4	3.525	1578.5	3.449	3191.9	6.974	829.5	1.812
M02023	465.8	1925.0	4.133	349.9	0.751	1271.3	2.729	11615.1	24.936	1679.1	3.605	1737.6	3.730	3416.7	7.335	765.8	1.644
M02024	461.7	1987.5	4.305	249.9	0.541	1443.6	3.127	12213.3	26.453	1738.2	3.765	1750.8	3.792	3489.0	7.557	772.8	1.674
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	449.2	1983.8	4.435	291.0	0.645	1355.1	3.020	11159.6	24.816	1513.4	3.382	1496.4	3.342	3009.7	6.724	752.1	1.675
S.D.	33.1	86.4	0.322	59.0	0.104	115.8	0.197	1131.8	1.230	138.0	0.350	154.2	0.359	282.2	0.689	100.1	0.186
Significance	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	DU	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
DU: Analysis by Dunnett's test.
KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 29-1-2(continued). Organ weights of male rats at the end of the dosing period

SF 15 mg/kg

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides		Prostate, ventral		Seminal vesicles		Thyroid gland	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M02013	1702.7	4.249	1751.4	4.371	3454.1	8.620	609.6	1.521	607.7	1.517	1217.3	3.038	627.2	1.565	2087.2	5.209	16.9	0.042
M02014	1598.0	3.870	1613.0	3.907	3211.0	7.777	585.0	1.417	611.5	1.481	1196.5	2.898	421.4	1.021	1547.6	3.748	22.4	0.054
M02015	1531.6	3.181	1502.9	3.121	3034.5	6.302	597.8	1.242	559.6	1.162	1157.4	2.404	884.0	1.836	1808.7	3.756	23.6	0.049
M02016	1593.0	3.382	1645.8	3.494	3238.8	6.876	646.6	1.373	620.0	1.316	1266.6	2.689	757.4	1.608	2051.7	4.356	20.8	0.044
M02017	1736.9	3.518	1711.1	3.466	3448.0	6.984	670.5	1.358	655.5	1.328	1326.0	2.686	479.7	0.972	1778.2	3.602	19.8	0.040
M02018	1668.3	3.504	1704.5	3.580	3372.8	7.084	565.4	1.188	600.4	1.261	1165.8	2.449	485.0	1.019	1509.4	3.170	24.2	0.051
M02019	1654.0	3.821	1644.8	3.799	3298.8	7.620	602.8	1.392	587.9	1.358	1190.7	2.751	495.1	1.144	1800.9	4.160	16.0	0.037
M02020	1445.3	3.249	1429.6	3.214	2874.9	6.463	549.7	1.236	556.3	1.251	1106.0	2.487	634.0	1.425	1436.4	3.229	19.3	0.043
M02021	1632.7	4.176	1665.4	4.259	3298.1	8.435	605.1	1.548	637.8	1.631	1242.9	3.179	659.4	1.686	1741.4	4.454	17.9	0.046
M02022	1637.2	3.577	1560.9	3.410	3198.1	6.987	615.3	1.344	560.9	1.225	1176.2	2.570	597.3	1.305	1646.0	3.596	19.4	0.042
M02023	1501.6	3.224	1554.9	3.338	3056.5	6.562	599.4	1.287	613.0	1.316	1212.4	2.603	568.2	1.220	2092.6	4.492	23.5	0.050
M02024	1680.0	3.639	1679.5	3.638	3359.5	7.276	689.5	1.493	665.7	1.442	1355.2	2.935	706.6	1.530	2209.0	4.784	19.3	0.042
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	1615.1	3.616	1622.0	3.633	3237.1	7.249	611.4	1.367	606.4	1.357	1217.8	2.724	609.6	1.361	1809.1	4.046	20.3	0.045
S.D.	86.0	0.354	94.0	0.389	175.7	0.738	40.4	0.116	36.1	0.136	71.0	0.244	132.4	0.289	253.3	0.631	2.7	0.005
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	DU	AN	AN	AN	DU	AN	KW	KW

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
DU: Analysis by Dunnett's test.
KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 29-1-2(continued). Organ weights of male rats at the end of the dosing period

SF 15 mg/kg

Male No.	Body weight (g)	Adrenal gland (R) (mg)	Adrenal gland (R) (mg/g)	Adrenal gland (L) (mg)	Adrenal gland (L) (mg/g)	Adrenal glands (mg)	Adrenal glands (mg/g)
M02013	400.7	22.6	0.056	25.6	0.064	48.2	0.120
M02014	412.9	25.6	0.062	25.9	0.063	51.5	0.125
M02015	481.5	21.1	0.044	23.0	0.048	44.1	0.092
M02016	471.0	36.3	0.077	38.6	0.082	74.9	0.159
M02017	493.7	26.7	0.054	30.7	0.062	57.4	0.116
M02018	476.1	35.2	0.074	36.2	0.076	71.4	0.150
M02019	432.9	28.5	0.066	29.5	0.068	58.0	0.134
M02020	444.8	26.6	0.060	26.8	0.060	53.4	0.120
M02021	391.0	23.6	0.060	25.6	0.065	49.2	0.126
M02022	457.7	24.9	0.054	25.8	0.056	50.7	0.111
M02023	465.8	26.2	0.056	28.7	0.062	54.9	0.118
M02024	461.7	32.4	0.070	32.8	0.071	65.2	0.141
Number of males	12	12	12	12	12	12	12
Mean	449.2	27.5	0.061	29.1	0.065	56.6	0.126
S.D.	33.1	4.8	0.009	4.7	0.009	9.5	0.018
Significance	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 29-1-3. Organ weights of male rats at the end of the dosing period

SF 50 mg/kg

Male No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M03025	446.5	2077.6	4.653	296.7	0.665	1514.3	3.391	10714.9	23.998	1434.8	3.213	1440.3	3.226	2875.1	6.439	795.3	1.781
M03026	439.4	1951.3	4.441	243.2	0.553	1375.2	3.130	11068.1	25.189	1732.6	3.943	1785.2	4.063	3517.8	8.006	702.1	1.598
M03027	427.7	1817.4	4.249	410.4	0.960	1336.7	3.125	11379.3	26.606	1557.9	3.643	1524.0	3.563	3081.9	7.206	829.5	1.939
M03028	445.1	2031.1	4.563	368.5	0.828	1308.0	2.939	11716.4	26.323	1560.6	3.506	1594.9	3.583	3155.5	7.089	905.4	2.034
M03029	477.9	1994.3	4.173	279.6	0.585	1497.2	3.133	12322.7	25.785	1554.7	3.253	1502.8	3.145	3057.5	6.398	869.8	1.820
M03030	473.7	2010.9	4.245	382.1	0.807	1462.4	3.087	13084.5	27.622	1687.7	3.563	1676.1	3.538	3363.8	7.101	1036.3	2.188
M03031	455.3	1908.0	4.191	252.2	0.554	1286.5	2.826	10778.5	23.673	1499.2	3.293	1449.0	3.183	2948.2	6.475	621.3	1.365
M03032	442.2	1981.5	4.481	224.6	0.508	1335.8	3.021	10593.8	23.957	1551.5	3.509	1512.7	3.421	3064.2	6.929	628.9	1.422
M03033	523.0	2003.4	3.831	305.5	0.584	1588.6	3.037	14427.2	27.585	1924.2	3.679	1955.3	3.739	3879.5	7.418	931.9	1.782
M03034	413.6	1951.4	4.718	211.1	0.510	1292.8	3.126	10059.8	24.323	1474.7	3.566	1514.3	3.661	2989.0	7.227	644.8	1.559
M03035	488.3	2027.4	4.152	241.9	0.495	1512.0	3.096	12350.7	25.293	1576.6	3.229	1564.0	3.203	3140.6	6.432	722.3	1.479
M03036	435.1	1996.8	4.589	263.6	0.606	1296.9	2.981	10360.5	23.812	1517.9	3.489	1375.9	3.162	2893.8	6.651	791.5	1.819
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	455.7	1979.3	4.357	290.0	0.638	1400.5	3.074	11571.4	25.347	1589.4	3.491	1574.5	3.457	3163.9	6.948	789.9	1.732
S.D.	30.2	67.2	0.260	65.1	0.149	107.3	0.137	1279.1	1.443	133.9	0.217	162.0	0.286	292.2	0.492	131.4	0.253
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	DU	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
DU: Analysis by Dunnett's test.
KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 29-1-3(continued). Organ weights of male rats at the end of the dosing period

SF 50 mg/kg

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides		Prostate, ventral		Seminal vesicles		Thyroid gland	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M03025	1574.0	3.525	1616.8	3.621	3190.8	7.146	606.8	1.359	610.8	1.368	1217.6	2.727	609.8	1.366	1914.6	4.288	26.3	0.059
M03026	1739.2	3.958	1764.3	4.015	3503.5	7.973	675.3	1.537	612.4	1.394	1287.7	2.931	703.6	1.601	1520.7	3.461	17.5	0.040
M03027	1378.8	3.224	1331.8	3.114	2710.6	6.338	592.9	1.386	593.1	1.387	1186.0	2.773	809.6	1.893	2020.0	4.723	24.1	0.056
M03028	1578.7	3.547	1581.6	3.553	3160.3	7.100	674.4	1.515	639.6	1.437	1314.0	2.952	886.2	1.991	2127.3	4.779	21.7	0.049
M03029	1493.7	3.126	1567.0	3.279	3060.7	6.404	606.3	1.269	588.6	1.232	1194.9	2.500	486.3	1.018	1994.7	4.174	17.0	0.036
M03030	1768.2	3.733	1816.1	3.834	3584.3	7.567	659.6	1.392	667.6	1.409	1327.2	2.802	658.4	1.390	2304.7	4.865	21.1	0.045
M03031	1811.1	3.978	1896.5	4.165	3707.6	8.143	653.9	1.436	695.7	1.528	1349.6	2.964	759.2	1.667	1970.1	4.327	17.2	0.038
M03032	1696.7	3.837	1732.6	3.918	3429.3	7.755	636.4	1.439	634.2	1.434	1270.6	2.873	554.4	1.254	1718.6	3.886	15.8	0.036
M03033	1490.8	2.850	1519.5	2.905	3010.3	5.756	689.7	1.319	648.1	1.239	1337.8	2.558	666.9	1.275	1691.0	3.233	19.4	0.037
M03034	1575.8	3.810	1562.0	3.777	3137.8	7.587	711.2	1.720	715.7	1.730	1426.9	3.450	502.8	1.216	1884.8	4.557	17.9	0.043
M03035	1770.6	3.626	1750.2	3.584	3520.8	7.210	664.5	1.361	639.9	1.310	1304.4	2.671	683.1	1.399	1640.9	3.360	18.7	0.038
M03036	1456.4	3.347	1398.6	3.214	2855.0	6.562	553.2	1.271	572.5	1.316	1125.7	2.587	457.2	1.051	1816.3	4.174	20.6	0.047
Number of males	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	1611.2	3.547	1628.1	3.582	3239.3	7.128	643.7	1.417	634.9	1.399	1278.5	2.816	648.1	1.427	1883.6	4.152	19.8	0.044
S.D.	142.6	0.351	169.1	0.387	309.5	0.732	45.7	0.127	43.1	0.134	84.0	0.254	132.8	0.307	220.7	0.561	3.1	0.008
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	DU	AN	AN	AN	DU	AN	KW	KW

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
DU: Analysis by Dunnett's test.
KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 29-1-3(continued). Organ weights of male rats at the end of the dosing period

SF 50 mg/kg

Male No.	Body weight (g)	Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M03025	446.5	26.9	0.060	28.2	0.063	55.1	0.123
M03026	439.4	26.8	0.061	28.6	0.065	55.4	0.126
M03027	427.7	29.0	0.068	28.9	0.068	57.9	0.135
M03028	445.1	27.0	0.061	27.7	0.062	54.7	0.123
M03029	477.9	27.7	0.058	31.1	0.065	58.8	0.123
M03030	473.7	27.9	0.059	30.8	0.065	58.7	0.124
M03031	455.3	23.0	0.051	24.1	0.053	47.1	0.103
M03032	442.2	25.0	0.057	23.5	0.053	48.5	0.110
M03033	523.0	25.3	0.048	26.3	0.050	51.6	0.099
M03034	413.6	26.2	0.063	28.7	0.069	54.9	0.133
M03035	488.3	29.1	0.060	32.4	0.066	61.5	0.126
M03036	435.1	34.8	0.080	33.2	0.076	68.0	0.156
Number of males	12	12	12	12	12	12	12
Mean	455.7	27.4	0.061	28.6	0.063	56.0	0.123
S.D.	30.2	2.9	0.008	3.0	0.008	5.7	0.015
Significance	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 29-1-4. Organ weights of male rats at the end of the dosing period

SF 150/75 mg/kg

Male No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04037	456.1	2046.9	4.488	292.5	0.641	1259.9	2.762	11341.2	24.866	1348.8	2.957	1355.3	2.971	2704.1	5.929	815.4	1.788
M04038	483.5	1914.9	3.960	257.9	0.533	1377.4	2.849	13398.1	27.711	1619.0	3.349	1562.3	3.231	3181.3	6.580	966.7	1.999
M04039	464.9	2030.0	4.367	338.1	0.727	1721.0	3.702	11568.3	24.883	1763.7	3.794	1720.4	3.701	3484.1	7.494	779.1	1.676
M04040	441.6	1989.5	4.505	263.3	0.596	1299.2	2.942	12147.5	27.508	1452.8	3.290	1471.3	3.332	2924.1	6.622	829.8	1.879
M04041	436.3	1938.2	4.442	200.3	0.459	1246.9	2.858	10436.5	23.920	1367.3	3.134	1521.1	3.486	2888.4	6.620	650.9	1.492
M04042	429.2	1977.8	4.608	325.8	0.759	1152.6	2.685	10261.7	23.909	1536.7	3.580	1547.0	3.604	3083.7	7.185	759.8	1.770
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	451.9	1982.9	4.395	279.7	0.619	1342.8	2.966	11525.6	25.466	1514.7	3.351	1529.6	3.388	3044.3	6.738	800.3	1.767
S.D.	20.2	51.0	0.227	50.5	0.114	199.2	0.371	1158.7	1.716	159.0	0.302	119.7	0.267	271.4	0.544	103.1	0.174
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	DU	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
DU: Analysis by Dunnett's test.
KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 29-1-4(continued). Organ weights of male rats at the end of the dosing period

SF 150/75 mg/kg

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides		Prostate, ventral		Seminal vesicles		Thyroid gland	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04037	1599.7	3.507	1584.5	3.474	3184.2	6.981	540.4	1.185	560.3	1.228	1100.7	2.413	441.0	0.967	1498.0	3.284	25.3	0.055
M04038	1584.1	3.276	1564.7	3.236	3148.8	6.513	612.8	1.267	599.0	1.239	1211.8	2.506	668.1	1.382	1381.7	2.858	14.6	0.030
M04039	1740.4	3.744	1707.3	3.672	3447.7	7.416	635.7	1.367	640.3	1.377	1276.0	2.745	559.0	1.202	1352.8	2.910	32.2	0.069
M04040	1492.1	3.379	1492.5	3.380	2984.6	6.759	577.3	1.307	593.0	1.343	1170.3	2.650	785.2	1.778	1583.7	3.586	14.7	0.033
M04041	1658.5	3.801	1647.4	3.776	3305.9	7.577	574.5	1.317	567.2	1.300	1141.7	2.617	677.0	1.552	1583.1	3.628	20.3	0.047
M04042	1529.2	3.563	1441.9	3.360	2971.1	6.922	614.5	1.432	608.8	1.418	1223.3	2.850	451.6	1.052	1795.9	4.184	19.9	0.046
Number of males	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Mean	1600.7	3.545	1573.1	3.483	3173.7	7.028	592.5	1.313	594.8	1.318	1187.3	2.630	597.0	1.322	1532.5	3.408	21.2	0.047
S.D.	89.5	0.203	97.4	0.204	184.4	0.401	34.7	0.084	29.1	0.076	62.7	0.158	137.0	0.309	161.7	0.500	6.7	0.014
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	DU	AN	AN	AN	DU	AN	KW	KW

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
DU: Analysis by Dunnett's test.
KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 29-1-4(continued). Organ weights of male rats at the end of the dosing period

SF 150/75 mg/kg

Male No.	Body weight (g)	Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04037	456.1	24.1	0.053	24.9	0.055	49.0	0.107
M04038	483.5	36.4	0.075	40.7	0.084	77.1	0.159
M04039	464.9	25.6	0.055	27.7	0.060	53.3	0.115
M04040	441.6	23.5	0.053	23.4	0.053	46.9	0.106
M04041	436.3	23.6	0.054	30.1	0.069	53.7	0.123
M04042	429.2	27.1	0.063	30.0	0.070	57.1	0.133
Number of males	6	6	6	6	6	6	6
Mean	451.9	26.7	0.059	29.5	0.065	56.2	0.124
S.D.	20.2	4.9	0.009	6.1	0.012	10.9	0.020
Significance	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 29-2-1. Organ weights of male rats at the end of the recovery period

Control (vehicle: water for injection)

Male No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01008	535.9	2035.8	3.799	266.8	0.498	1479.8	2.761	12931.6	24.131	1685.3	3.145	1661.4	3.100	3346.7	6.245	737.2	1.376
M01009	482.4	2142.5	4.441	191.9	0.398	1412.9	2.929	11796.6	24.454	1533.5	3.179	1704.7	3.534	3238.2	6.713	681.6	1.413
M01010	465.2	2096.7	4.507	334.8	0.720	1434.1	3.083	12602.8	27.091	1409.4	3.030	1410.9	3.033	2820.3	6.063	730.8	1.571
M01011	462.2	2057.9	4.452	300.8	0.651	1492.0	3.228	10000.2	21.636	1421.7	3.076	1470.9	3.182	2892.6	6.258	867.5	1.877
M01012	451.8	1948.9	4.314	341.7	0.756	1423.5	3.151	11759.0	26.027	1456.3	3.223	1448.7	3.207	2905.0	6.430	926.3	2.050
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	479.5	2056.4	4.303	287.2	0.605	1448.5	3.030	11818.0	24.668	1501.2	3.131	1539.3	3.211	3040.6	6.342	788.7	1.657
S.D.	33.4	72.5	0.290	61.1	0.152	35.3	0.187	1136.3	2.076	113.7	0.078	133.8	0.193	235.4	0.245	103.2	0.295

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 29-2-1(continued). Organ weights of male rats at the end of the recovery period

Control (vehicle: water for injection)

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides		Prostate, ventral		Seminal vesicles		Thyroid gland	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01008	1470.9	2.745	1549.8	2.892	3020.7	5.637	597.5	1.115	607.6	1.134	1205.1	2.249	365.7	0.682	2072.7	3.868	19.2	0.036
M01009	1518.8	3.148	1584.3	3.284	3103.1	6.433	574.0	1.190	591.1	1.225	1165.1	2.415	430.6	0.893	1465.7	3.038	21.7	0.045
M01010	1698.5	3.651	1679.2	3.610	3377.7	7.261	658.6	1.416	613.0	1.318	1271.6	2.733	509.3	1.095	1536.7	3.303	19.5	0.042
M01011	1805.8	3.907	1799.8	3.894	3605.6	7.801	731.6	1.583	736.7	1.594	1468.3	3.177	569.4	1.232	1372.3	2.969	22.5	0.049
M01012	1861.9	4.121	1848.0	4.090	3709.9	8.211	724.7	1.604	682.5	1.511	1407.2	3.115	770.5	1.705	1624.4	3.595	20.6	0.046
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	1671.2	3.514	1692.2	3.554	3363.4	7.069	657.3	1.382	646.2	1.356	1303.5	2.738	529.1	1.121	1614.4	3.355	20.7	0.044
S.D.	172.2	0.563	130.3	0.479	301.7	1.041	71.7	0.223	61.5	0.193	130.2	0.412	155.5	0.387	272.4	0.378	1.4	0.005

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 29-2-1(continued). Organ weights of male rats at the end of the recovery period

Control (vehicle: water for injection)

Male No.	Body weight (g)	Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
		(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M01008	535.9	24.1	0.045	26.5	0.049	50.6	0.094
M01009	482.4	25.7	0.053	27.0	0.056	52.7	0.109
M01010	465.2	27.6	0.059	29.7	0.064	57.3	0.123
M01011	462.2	29.3	0.063	28.3	0.061	57.6	0.125
M01012	451.8	25.5	0.056	24.4	0.054	49.9	0.110
Number of males	5	5	5	5	5	5	5
Mean	479.5	26.4	0.055	27.2	0.057	53.6	0.112
S.D.	33.4	2.0	0.007	2.0	0.006	3.6	0.013

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 29-2-2. Organ weights of male rats at the end of the recovery period

SF 150/75 mg/kg

Male No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04043	522.9	2126.5	4.067	322.2	0.616	1503.4	2.875	12431.6	23.774	1524.9	2.916	1512.0	2.892	3036.9	5.808	768.7	1.470
M04044	483.4	1990.1	4.117	368.7	0.763	1462.3	3.025	13054.1	27.005	1650.5	3.414	1738.7	3.597	3389.2	7.011	917.8	1.899
M04045	409.8	1910.3	4.662	217.7	0.531	1278.4	3.120	9621.1	23.478	1305.2	3.185	1329.2	3.244	2634.4	6.429	740.8	1.808
M04047	461.7	2033.4	4.404	152.5	0.330	1247.8	2.703	10948.6	23.714	1616.1	3.500	1467.8	3.179	3083.9	6.679	708.8	1.535
M04048	498.3	2183.4	4.382	208.5	0.418	1482.1	2.974	12530.6	25.147	1419.8	2.849	1489.4	2.989	2909.2	5.838	1009.7	2.026
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	475.2	2048.7	4.326	253.9	0.532	1394.8	2.939	11717.2	24.624	1503.3	3.173	1507.4	3.180	3010.7	6.353	829.2	1.748
S.D.	42.8	108.4	0.241	88.7	0.169	121.6	0.159	1409.2	1.484	142.4	0.290	147.6	0.273	274.4	0.526	128.8	0.238
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	AW	TT	TT	TT	TT	AW	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.
AW: Analysis by Aspin-Welch t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 29-2-2(continued). Organ weights of male rats at the end of the recovery period

SF 150/75 mg/kg

Male No.	Testis (R)		Testis (L)		Testes		Epididymis (R)		Epididymis (L)		Epididymides		Prostate, ventral		Seminal vesicles		Thyroid gland	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
M04043	1461.5	2.795	1404.9	2.687	2866.4	5.482	513.7	0.982	537.6	1.028	1051.3	2.011	584.0	1.117	1486.4	2.843	20.0	0.038
M04044	1236.6	2.558	1197.2	2.477	2433.8	5.035	562.1	1.163	566.5	1.172	1128.6	2.335	837.1	1.732	1671.5	3.458	19.8	0.041
M04045	1646.2	4.017	1676.0	4.090	3322.2	8.107	607.7	1.483	661.6	1.614	1269.3	3.097	628.9	1.535	1691.9	4.129	19.2	0.047
M04047	1827.2	3.958	1745.4	3.780	3572.6	7.738	704.9	1.527	706.9	1.531	1411.8	3.058	716.2	1.551	1789.5	3.876	21.8	0.047
M04048	1703.8	3.419	1727.9	3.468	3431.7	6.887	637.9	1.280	632.8	1.270	1270.7	2.550	602.2	1.209	1512.1	3.035	16.4	0.033
Number of males	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	1575.1	3.349	1550.3	3.300	3125.3	6.650	605.3	1.287	621.1	1.323	1226.3	2.610	673.7	1.429	1630.3	3.468	19.4	0.041
S.D.	230.6	0.662	240.4	0.696	468.5	1.354	72.9	0.226	69.1	0.245	140.0	0.468	104.5	0.257	128.0	0.544	2.0	0.006
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.
AW: Analysis by Aspin-Welch t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 29-2-2(continued). Organ weights of male rats at the end of the recovery period

SF 150/75 mg/kg

Male No.	Body weight (g)	Adrenal gland (R) (mg)	Adrenal gland (R) (mg/g)	Adrenal gland (L) (mg)	Adrenal gland (L) (mg/g)	Adrenal glands (mg)	Adrenal glands (mg/g)
M04043	522.9	31.1	0.059	29.0	0.055	60.1	0.115
M04044	483.4	26.1	0.054	25.6	0.053	51.7	0.107
M04045	409.8	27.4	0.067	27.8	0.068	55.2	0.135
M04047	461.7	26.4	0.057	29.6	0.064	56.0	0.121
M04048	498.3	28.2	0.057	29.7	0.060	57.9	0.116
Number of males	5	5	5	5	5	5	5
Mean	475.2	27.8	0.059	28.3	0.060	56.2	0.119
S.D.	42.8	2.0	0.005	1.7	0.006	3.1	0.010
Significance	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 30-1-1. Organ weights of female rats at the end of the dosing period

Control (vehicle: water for injection)

Female No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F01001	303.5	1841.0	6.066	212.8	0.701	1077.5	3.550	9505.4	31.319	853.0	2.811	997.7	3.287	1850.7	6.098	878.0	2.893
F01002	275.6	1826.9	6.629	142.5	0.517	882.7	3.203	9039.5	32.799	990.4	3.594	930.6	3.377	1921.0	6.970	674.4	2.447
F01003	276.7	1928.2	6.969	205.7	0.743	986.6	3.566	9413.0	34.019	1010.4	3.652	998.8	3.610	2009.2	7.261	606.4	2.192
F01004	267.8	1839.2	6.868	187.3	0.699	875.4	3.269	8934.7	33.363	842.7	3.147	789.1	2.947	1631.8	6.093	806.3	3.011
F01005	313.6	1790.5	5.710	315.3	1.005	1069.3	3.410	9828.5	31.341	1095.3	3.493	1079.2	3.441	2174.5	6.934	712.2	2.271
F01006	291.3	1908.6	6.552	154.9	0.532	1014.6	3.483	10137.5	34.801	1034.1	3.550	917.5	3.150	1951.6	6.700	1032.5	3.544
F01007	295.8	1905.4	6.442	178.9	0.605	985.1	3.330	9304.8	31.456	1008.2	3.408	1009.0	3.411	2017.2	6.819	611.6	2.068
F01008	316.6	1932.6	6.104	199.5	0.630	1222.9	3.863	10328.4	32.623	1040.3	3.286	1077.0	3.402	2117.3	6.688	641.9	2.027
F01009	268.9	1863.6	6.930	145.2	0.540	903.7	3.361	8025.0	29.844	930.8	3.462	945.5	3.516	1876.3	6.978	478.8	1.781
F01010	274.8	1899.3	6.912	184.4	0.671	927.8	3.376	8891.2	32.355	926.6	3.372	906.5	3.299	1833.1	6.671	619.5	2.254
F01012	285.7	1918.7	6.716	203.8	0.713	959.6	3.359	10006.5	35.025	1093.9	3.829	1075.3	3.764	2169.2	7.593	733.5	2.567
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	288.2	1877.6	6.536	193.7	0.669	991.4	3.434	9401.3	32.631	984.2	3.419	975.1	3.382	1959.3	6.800	708.6	2.460
S.D.	17.4	47.6	0.416	47.2	0.137	102.8	0.180	668.8	1.598	86.4	0.272	88.9	0.219	162.7	0.442	151.7	0.513

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 30-1-1(continued). Organ weights of female rats at the end of the dosing period

Control (vehicle: water for injection)

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F01001	51.7	0.170	46.3	0.153	98.0	0.323	709.2	2.337	11.5	0.038	27.0	0.089	32.2	0.106	59.2	0.195
F01002	45.5	0.165	45.2	0.164	90.7	0.329	706.3	2.563	12.7	0.046	37.8	0.137	37.7	0.137	75.5	0.274
F01003	51.4	0.186	46.3	0.167	97.7	0.353	516.9	1.868	14.1	0.051	39.2	0.142	43.0	0.155	82.2	0.297
F01004	58.7	0.219	50.4	0.188	109.1	0.407	583.1	2.177	20.0	0.075	29.8	0.111	30.2	0.113	60.0	0.224
F01005	65.2	0.208	65.0	0.207	130.2	0.415	604.0	1.926	15.0	0.048	39.7	0.127	42.9	0.137	82.6	0.263
F01006	59.3	0.204	50.9	0.175	110.2	0.378	743.1	2.551	26.3	0.090	35.8	0.123	37.0	0.127	72.8	0.250
F01007	50.9	0.172	53.5	0.181	104.4	0.353	656.2	2.218	13.7	0.046	40.8	0.138	41.4	0.140	82.2	0.278
F01008	53.1	0.168	52.1	0.165	105.2	0.332	705.4	2.228	17.7	0.056	38.5	0.122	41.1	0.130	79.6	0.251
F01009	44.3	0.165	37.8	0.141	82.1	0.305	529.0	1.967	15.2	0.057	33.1	0.123	37.6	0.140	70.7	0.263
F01010	40.3	0.147	48.0	0.175	88.3	0.321	560.9	2.041	15.3	0.056	35.3	0.128	34.6	0.126	69.9	0.254
F01012	66.9	0.234	34.0	0.119	100.9	0.353	632.0	2.212	11.3	0.040	32.9	0.115	32.6	0.114	65.5	0.229
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	53.4	0.185	48.1	0.167	101.5	0.352	631.5	2.190	15.7	0.055	35.4	0.123	37.3	0.130	72.7	0.253
S.D.	8.5	0.027	8.1	0.024	12.9	0.036	78.7	0.232	4.3	0.015	4.4	0.015	4.5	0.014	8.6	0.028

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 30-1-2. Organ weights of female rats at the end of the dosing period

SF 15 mg/kg

Female No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F02013	311.2	1971.1	6.334	226.4	0.728	987.9	3.174	9253.5	29.735	962.5	3.093	984.5	3.164	1947.0	6.256	712.9	2.291
F02014	305.7	1964.6	6.427	192.5	0.630	954.2	3.121	9818.6	32.118	1041.7	3.408	1010.3	3.305	2052.0	6.712	584.0	1.910
F02015	287.7	1944.3	6.758	242.3	0.842	1022.8	3.555	9859.4	34.270	1102.2	3.831	1069.4	3.717	2171.6	7.548	676.4	2.351
F02016	294.6	1816.1	6.165	256.8	0.872	1011.3	3.433	9625.3	32.672	1049.0	3.561	998.0	3.388	2047.0	6.948	995.4	3.379
F02017	254.8	1817.7	7.134	134.0	0.526	823.5	3.232	9157.7	35.941	968.3	3.800	969.1	3.803	1937.4	7.604	608.6	2.389
F02018	280.5	1899.2	6.771	184.0	0.656	906.2	3.231	9440.5	33.656	975.6	3.478	914.3	3.260	1889.9	6.738	746.0	2.660
F02019	324.8	1893.1	5.829	268.6	0.827	1080.7	3.327	10353.6	31.877	1018.4	3.135	1037.9	3.196	2056.3	6.331	727.2	2.239
F02020	286.8	1956.7	6.823	204.2	0.712	975.2	3.400	9605.9	33.493	1090.3	3.802	1127.2	3.930	2217.5	7.732	642.5	2.240
F02021	292.2	1898.0	6.496	106.4	0.364	1023.9	3.504	8566.4	29.317	994.4	3.403	954.8	3.268	1949.2	6.671	519.5	1.778
F02022	266.3	1873.2	7.034	223.4	0.839	931.5	3.498	9010.3	33.835	899.6	3.378	900.2	3.380	1799.8	6.759	841.9	3.161
F02023	287.0	1852.0	6.453	176.9	0.616	904.1	3.150	9553.5	33.287	975.9	3.400	973.9	3.393	1949.8	6.794	736.3	2.566
F02024	283.6	1851.8	6.530	219.7	0.775	888.7	3.134	9102.9	32.098	927.6	3.271	963.6	3.398	1891.2	6.669	750.2	2.645
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	289.6	1894.8	6.563	202.9	0.699	959.2	3.313	9445.6	32.692	1000.5	3.463	991.9	3.434	1992.4	6.897	711.7	2.467
S.D.	18.8	55.0	0.367	47.9	0.150	71.9	0.159	467.5	1.853	61.8	0.247	63.5	0.248	120.6	0.481	124.6	0.460
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	KW	AN	KW	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 30-1-2(continued). Organ weights of female rats at the end of the dosing period

SF 15 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F02013	48.7	0.156	51.0	0.164	99.7	0.320	596.0	1.915	12.9	0.041	31.9	0.103	34.9	0.112	66.8	0.215
F02014	46.6	0.152	47.8	0.156	94.4	0.309	671.5	2.197	11.7	0.038	30.3	0.099	30.6	0.100	60.9	0.199
F02015	48.8	0.170	50.6	0.176	99.4	0.345	538.7	1.872	18.1	0.063	44.4	0.154	45.9	0.160	90.3	0.314
F02016	50.5	0.171	51.2	0.174	101.7	0.345	953.2	3.236	16.6	0.056	36.6	0.124	37.4	0.127	74.0	0.251
F02017	43.6	0.171	69.3	0.272	112.9	0.443	506.8	1.989	13.3	0.052	35.2	0.138	41.0	0.161	76.2	0.299
F02018	56.1	0.200	58.2	0.207	114.3	0.407	451.8	1.611	9.4	0.034	37.1	0.132	39.8	0.142	76.9	0.274
F02019	50.9	0.157	58.6	0.180	109.5	0.337	697.1	2.146	11.5	0.035	48.5	0.149	43.6	0.134	92.1	0.284
F02020	46.3	0.161	44.2	0.154	90.5	0.316	614.9	2.144	15.8	0.055	37.1	0.129	38.2	0.133	75.3	0.263
F02021	37.3	0.128	32.2	0.110	69.5	0.238	506.6	1.734	13.9	0.048	27.4	0.094	29.6	0.101	57.0	0.195
F02022	58.8	0.221	50.7	0.190	109.5	0.411	555.9	2.087	13.1	0.049	27.5	0.103	33.5	0.126	61.0	0.229
F02023	56.9	0.198	63.3	0.221	120.2	0.419	510.0	1.777	15.8	0.055	40.3	0.140	41.5	0.145	81.8	0.285
F02024	48.1	0.170	60.2	0.212	108.3	0.382	534.9	1.886	14.8	0.052	32.8	0.116	36.4	0.128	69.2	0.244
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	49.4	0.171	53.1	0.185	102.5	0.356	594.8	2.050	13.9	0.048	35.8	0.123	37.7	0.131	73.5	0.254
S.D.	6.0	0.025	9.7	0.041	13.5	0.058	133.7	0.415	2.4	0.009	6.4	0.020	5.0	0.020	11.2	0.039
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	KW	DU	AN	AN	KW	DU

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 30-1-3. Organ weights of female rats at the end of the dosing period

SF 50 mg/kg

Female No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F03025	296.8	1819.0	6.129	347.2	1.170	978.7	3.298	9403.6	31.683	1126.4	3.795	1114.1	3.754	2240.5	7.549	728.0	2.453
F03026	289.0	1814.5	6.279	140.6	0.487	982.2	3.399	9296.4	32.167	878.9	3.041	946.1	3.274	1825.0	6.315	786.1	2.720
F03027	279.7	1882.6	6.731	178.3	0.637	883.9	3.160	8651.5	30.931	965.1	3.450	904.9	3.235	1870.0	6.686	639.6	2.287
F03028	320.4	1928.8	6.020	190.7	0.595	961.1	3.000	9481.9	29.594	1187.1	3.705	1063.4	3.319	2250.5	7.024	543.8	1.697
F03029	315.5	1854.4	5.878	174.7	0.554	951.2	3.015	9596.2	30.416	1015.4	3.218	969.7	3.074	1985.1	6.292	589.5	1.868
F03030	272.6	1900.9	6.973	186.8	0.685	999.3	3.666	8395.9	30.799	904.5	3.318	921.2	3.379	1825.7	6.697	706.4	2.591
F03031	296.9	1888.1	6.359	274.1	0.923	916.4	3.087	9463.4	31.874	1038.2	3.497	1050.5	3.538	2088.7	7.035	741.2	2.496
F03032	288.7	1911.9	6.622	145.3	0.503	907.4	3.143	10038.6	34.772	1022.7	3.542	1002.2	3.471	2024.9	7.014	785.9	2.722
F03033	278.5	1779.8	6.391	200.5	0.720	966.7	3.471	9641.3	34.619	974.0	3.497	985.5	3.539	1959.5	7.036	625.4	2.246
F03034	312.9	1877.7	6.001	165.6	0.529	978.9	3.128	10213.7	32.642	942.7	3.013	939.0	3.001	1881.7	6.014	591.3	1.890
F03035	348.9	1819.6	5.215	214.4	0.615	1115.6	3.197	10389.7	29.778	1099.9	3.152	1051.0	3.012	2150.9	6.165	823.0	2.359
F03036	283.4	1876.2	6.620	232.3	0.820	957.0	3.377	11965.9	42.223	1149.4	4.056	1076.1	3.797	2225.5	7.853	678.9	2.396
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	298.6	1862.8	6.268	204.2	0.687	966.5	3.245	9711.5	32.625	1025.4	3.440	1002.0	3.366	2027.3	6.807	686.6	2.310
S.D.	22.1	45.5	0.467	58.2	0.200	58.0	0.201	912.3	3.448	98.5	0.314	68.1	0.266	161.7	0.557	89.6	0.335
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	KW	AN	KW	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 30-1-3(continued). Organ weights of female rats at the end of the dosing period

SF 50 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F03025	48.2	0.162	50.9	0.171	99.1	0.334	739.7	2.492	11.7	0.039	39.1	0.132	41.8	0.141	80.9	0.273
F03026	65.0	0.225	46.2	0.160	111.2	0.385	554.7	1.919	15.2	0.053	38.2	0.132	39.0	0.135	77.2	0.267
F03027	52.1	0.186	56.9	0.203	109.0	0.390	617.4	2.207	8.1	0.029	34.6	0.124	36.2	0.129	70.8	0.253
F03028	55.3	0.173	40.5	0.126	95.8	0.299	626.1	1.954	12.9	0.040	37.6	0.117	35.6	0.111	73.2	0.228
F03029	41.7	0.132	50.3	0.159	92.0	0.292	599.4	1.900	12.9	0.041	38.9	0.123	40.2	0.127	79.1	0.251
F03030	56.1	0.206	45.6	0.167	101.7	0.373	603.8	2.215	17.4	0.064	31.4	0.115	36.6	0.134	68.0	0.249
F03031	42.6	0.143	42.9	0.144	85.5	0.288	498.2	1.678	12.7	0.043	35.7	0.120	35.5	0.120	71.2	0.240
F03032	44.9	0.156	54.4	0.188	99.3	0.344	675.0	2.338	15.4	0.053	36.6	0.127	36.9	0.128	73.5	0.255
F03033	46.5	0.167	45.6	0.164	92.1	0.331	548.4	1.969	18.1	0.065	39.3	0.141	39.0	0.140	78.3	0.281
F03034	73.6	0.235	39.7	0.127	113.3	0.362	572.6	1.830	16.1	0.051	39.9	0.128	35.8	0.114	75.7	0.242
F03035	52.9	0.152	57.4	0.165	110.3	0.316	635.3	1.821	17.0	0.049	35.8	0.103	34.4	0.099	70.2	0.201
F03036	65.9	0.233	61.6	0.217	127.5	0.450	685.0	2.417	16.4	0.058	37.4	0.132	44.9	0.158	82.3	0.290
Number of females	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12	12
Mean	53.7	0.181	49.3	0.166	103.1	0.347	613.0	2.062	14.5	0.049	37.0	0.125	38.0	0.128	75.0	0.253
S.D.	10.0	0.036	7.1	0.027	11.6	0.048	66.3	0.262	2.9	0.011	2.4	0.010	3.1	0.016	4.6	0.024
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	KW	DU	AN	AN	KW	DU

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 30-1-4. Organ weights of female rats at the end of the dosing period

SF 150/75 mg/kg

Female No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F04037	283.8	1888.7	6.655	258.3	0.910	881.8	3.107	10088.2	35.547	886.4	3.123	882.7	3.110	1769.1	6.234	628.2	2.214
F04038	296.6	1870.6	6.307	164.7	0.555	850.0	2.866	9763.4	32.918	1056.1	3.561	1044.5	3.522	2100.6	7.082	757.7	2.555
F04039	262.5	1799.5	6.855	93.6	0.357	915.9	3.489	8450.8	32.194	908.0	3.459	959.6	3.656	1867.6	7.115	600.0	2.286
F04040	259.7	1781.7	6.861	50.2	0.193	873.2	3.362	8635.8	33.253	1098.2	4.229	1060.7	4.084	2158.9	8.313	640.1	2.465
F04041	280.2	1910.7	6.819	186.3	0.665	1178.5	4.206	9862.4	35.198	952.5	3.399	964.7	3.443	1917.2	6.842	662.4	2.364
F04042	265.1	1981.8	7.476	191.9	0.724	831.0	3.135	8751.3	33.011	867.4	3.272	882.6	3.329	1750.0	6.601	619.3	2.336
F04043	287.3	1861.9	6.481	134.3	0.467	1120.8	3.901	9790.7	34.078	1127.5	3.924	1054.4	3.670	2181.9	7.595	784.4	2.730
F04044	288.2	1845.6	6.404	224.0	0.777	1023.1	3.550	10467.0	36.319	1059.1	3.675	1108.5	3.846	2167.6	7.521	843.8	2.928
F04045	288.6	1792.6	6.211	242.1	0.839	963.5	3.339	9226.6	31.970	1020.9	3.537	954.1	3.306	1975.0	6.843	637.3	2.208
F04047	286.7	1886.4	6.580	207.5	0.724	891.9	3.111	9804.7	34.198	1054.2	3.677	1084.4	3.782	2138.6	7.459	574.4	2.003
F04048	295.3	1884.0	6.380	175.9	0.596	1073.8	3.636	10498.5	35.552	1115.1	3.776	1097.2	3.716	2212.3	7.492	633.3	2.145
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	281.3	1864.0	6.639	175.3	0.619	964.0	3.427	9576.3	34.022	1013.2	3.603	1008.5	3.588	2021.7	7.191	671.0	2.385
S.D.	13.0	58.3	0.357	62.7	0.214	118.0	0.388	712.4	1.475	94.0	0.307	82.9	0.279	172.2	0.567	85.3	0.269
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	AN	AN	AN	AN	AN	AN	KW	AN	KW	AN	AN	AN	AN	AN	AN	AN	AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 30-1-4(continued). Organ weights of female rats at the end of the dosing period

SF 150/75 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F04037	46.1	0.162	52.3	0.184	98.4	0.347	466.1	1.642	14.0	0.049	45.2	0.159	43.1	0.152	88.3	0.311
F04038	47.6	0.160	55.4	0.187	103.0	0.347	710.9	2.397	15.6	0.053	35.1	0.118	34.9	0.118	70.0	0.236
F04039	46.0	0.175	46.2	0.176	92.2	0.351	520.3	1.982	11.4	0.043	33.4	0.127	33.9	0.129	67.3	0.256
F04040	62.6	0.241	54.7	0.211	117.3	0.452	710.1	2.734	17.1	0.066	43.9	0.169	45.0	0.173	88.9	0.342
F04041	44.0	0.157	45.1	0.161	89.1	0.318	515.8	1.841	11.7	0.042	39.1	0.140	41.0	0.146	80.1	0.286
F04042	52.8	0.199	54.5	0.206	107.3	0.405	383.7	1.447	13.2	0.050	37.4	0.141	37.5	0.141	74.9	0.283
F04043	38.4	0.134	59.4	0.207	97.8	0.340	613.9	2.137	12.1	0.042	39.4	0.137	43.8	0.152	83.2	0.290
F04044	68.1	0.236	46.1	0.160	114.2	0.396	568.0	1.971	9.5	0.033	38.9	0.135	39.6	0.137	78.5	0.272
F04045	54.5	0.189	56.1	0.194	110.6	0.383	605.8	2.099	12.5	0.043	40.8	0.141	40.2	0.139	81.0	0.281
F04047	48.1	0.168	49.1	0.171	97.2	0.339	584.0	2.037	18.2	0.063	40.4	0.141	38.3	0.134	78.7	0.275
F04048	52.7	0.178	49.4	0.167	102.1	0.346	512.2	1.735	17.4	0.059	45.6	0.154	42.8	0.145	88.4	0.299
Number of females	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11	11
Mean	51.0	0.182	51.7	0.184	102.7	0.366	562.8	2.002	13.9	0.049	39.9	0.142	40.0	0.142	79.9	0.285
S.D.	8.5	0.033	4.8	0.019	8.9	0.039	98.3	0.355	2.8	0.010	3.9	0.014	3.6	0.014	7.2	0.028
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	*	NS	NS	NS	*
Statistical method	AN	AN	AN	AN	AN	AN	AN	AN	AN	AN	KW	DU	AN	AN	KW	DU

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
KW: Analysis by Kruskal-Wallis' test (one-way layout).
DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 30-2-1. Organ weights of female rats at the end of the dosing period, satellite group

Control (vehicle: water for injection)

Female No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05049	272.0	1799.0	6.614	284.6	1.046	892.7	3.282	6218.1	22.861	896.8	3.297	857.6	3.153	1754.4	6.450	538.3	1.979
F05050	256.7	1791.3	6.978	308.6	1.202	791.6	3.084	6343.0	24.710	900.2	3.507	870.8	3.392	1771.0	6.899	583.3	2.272
F05051	279.3	1890.4	6.768	385.6	1.381	941.4	3.371	7412.7	26.540	886.3	3.173	860.3	3.080	1746.6	6.253	582.3	2.085
F05052	249.5	1824.1	7.311	337.1	1.351	810.2	3.247	7064.7	28.315	939.6	3.766	913.2	3.660	1852.8	7.426	570.9	2.288
F05053	240.1	1854.7	7.725	240.0	1.000	811.0	3.378	6061.5	25.246	883.5	3.680	875.4	3.646	1758.9	7.326	514.8	2.144
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	259.5	1831.9	7.079	311.2	1.196	849.4	3.272	6620.0	25.534	901.3	3.485	875.5	3.386	1776.7	6.871	557.9	2.154
S.D.	16.1	41.0	0.446	54.7	0.173	64.6	0.119	586.6	2.040	22.5	0.250	22.3	0.270	43.4	0.518	30.2	0.130

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 30-2-1(continued). Organ weights of female rats at the end of the dosing period, satellite group

Control (vehicle: water for injection)

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05049	54.5	0.200	53.6	0.197	108.1	0.397	473.1	1.739	14.3	0.053	28.6	0.105	29.0	0.107	57.6	0.212
F05050	36.7	0.143	48.6	0.189	85.3	0.332	672.2	2.619	13.8	0.054	37.0	0.144	37.5	0.146	74.5	0.290
F05051	51.8	0.185	50.5	0.181	102.3	0.366	501.1	1.794	20.4	0.073	32.2	0.115	34.4	0.123	66.6	0.238
F05052	43.9	0.176	35.0	0.140	78.9	0.316	428.2	1.716	15.1	0.061	29.6	0.119	35.1	0.141	64.7	0.259
F05053	31.0	0.129	38.4	0.160	69.4	0.289	761.0	3.170	10.9	0.045	34.4	0.143	34.7	0.145	69.1	0.288
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	43.6	0.167	45.2	0.173	88.8	0.340	567.1	2.208	14.9	0.057	32.4	0.125	34.1	0.132	66.5	0.257
S.D.	9.9	0.030	8.1	0.023	16.1	0.042	142.4	0.657	3.5	0.010	3.4	0.017	3.1	0.017	6.2	0.033

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 30-2-2. Organ weights of female rats at the end of the dosing period, satellite group

SF 150/75 mg/kg

Female No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F06059	232.2	1836.5	7.909	414.6	1.786	751.4	3.236	6202.1	26.710	824.0	3.549	861.0	3.708	1685.0	7.257	449.3	1.935
F06064	260.5	1949.1	7.482	165.2	0.634	802.0	3.079	7317.0	28.088	907.7	3.484	858.2	3.294	1765.9	6.779	638.2	2.450
F06065	253.5	1839.5	7.256	221.9	0.875	823.1	3.247	8038.4	31.710	1071.1	4.225	1022.4	4.033	2093.5	8.258	523.5	2.065
Number of females	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Mean	248.7	1875.0	7.549	267.2	1.098	792.2	3.187	7185.8	28.836	934.3	3.753	913.9	3.678	1848.1	7.431	537.0	2.150
S.D.	14.7	64.2	0.332	130.7	0.608	36.8	0.094	925.2	2.583	125.7	0.410	94.0	0.370	216.3	0.755	95.2	0.268
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	AW	TT	TT	TT	TT	AW	TT	AW	TT	AW	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.
AW: Analysis by Aspin-Welch t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 30-2-2(continued). Organ weights of female rats at the end of the dosing period, satellite group

SF 150/75 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F06059	55.6	0.239	43.9	0.189	99.5	0.429	602.2	2.593	14.0	0.060	28.2	0.121	30.7	0.132	58.9	0.254
F06064	49.6	0.190	36.5	0.140	86.1	0.331	559.3	2.147	13.2	0.051	29.3	0.112	31.9	0.122	61.2	0.235
F06065	55.3	0.218	55.6	0.219	110.9	0.437	483.0	1.905	15.3	0.060	24.8	0.098	29.7	0.117	54.5	0.215
Number of females	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Mean	53.5	0.216	45.3	0.183	98.8	0.399	548.2	2.215	14.2	0.057	27.4	0.110	30.8	0.124	58.2	0.235
S.D.	3.4	0.025	9.6	0.040	12.4	0.059	60.4	0.349	1.1	0.005	2.3	0.012	1.1	0.008	3.4	0.020
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.
AW: Analysis by Aspin-Welch t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 30-3-1. Organ weights of female rats at the end of the recovery period

Control (vehicle: water for injection)

Female No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05054	279.9	1851.0	6.613	301.0	1.075	933.2	3.334	7547.0	26.963	879.6	3.143	884.2	3.159	1763.8	6.302	601.8	2.150
F05055	307.7	1883.2	6.120	331.0	1.076	963.4	3.131	7929.9	25.772	1043.9	3.393	971.4	3.157	2015.3	6.550	566.5	1.841
F05056	279.2	1750.6	6.270	216.7	0.776	1002.6	3.591	7066.6	25.310	892.8	3.198	846.5	3.032	1739.3	6.230	565.9	2.027
F05057	244.6	1764.2	7.213	232.5	0.951	794.9	3.250	6077.1	24.845	954.1	3.901	909.0	3.716	1863.1	7.617	493.6	2.018
F05058	269.9	1859.9	6.891	236.7	0.877	797.6	2.955	7202.8	26.687	964.6	3.574	898.2	3.328	1862.8	6.902	640.7	2.374
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	276.3	1821.8	6.621	263.6	0.951	898.3	3.252	7164.7	25.915	947.0	3.442	901.9	3.278	1848.9	6.720	573.7	2.082
S.D.	22.7	60.1	0.447	49.6	0.130	96.4	0.237	693.8	0.898	65.6	0.308	45.5	0.266	108.8	0.566	54.3	0.197

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 30-3-1(continued). Organ weights of female rats at the end of the recovery period

Control (vehicle: water for injection)

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F05054	59.1	0.211	53.4	0.191	112.5	0.402	469.0	1.676	35.2	0.126	36.8	0.131	39.5	0.141	76.3	0.273
F05055	53.8	0.175	50.7	0.165	104.5	0.340	572.8	1.862	16.2	0.053	31.4	0.102	31.9	0.104	63.3	0.206
F05056	45.0	0.161	51.3	0.184	96.3	0.345	528.5	1.893	18.2	0.065	32.0	0.115	32.6	0.117	64.6	0.231
F05057	32.5	0.133	32.4	0.132	64.9	0.265	525.1	2.147	17.2	0.070	31.2	0.128	33.0	0.135	64.2	0.262
F05058	45.7	0.169	44.5	0.165	90.2	0.334	530.3	1.965	17.1	0.063	45.0	0.167	50.4	0.187	95.4	0.353
Number of females	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5	5
Mean	47.2	0.170	46.5	0.167	93.7	0.337	525.1	1.909	20.8	0.075	35.3	0.129	37.5	0.137	72.8	0.265
S.D.	10.1	0.028	8.5	0.023	18.2	0.049	36.9	0.171	8.1	0.029	5.9	0.024	7.8	0.032	13.7	0.056

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 30-3-2. Organ weights of female rats at the end of the recovery period

SF 150/75 mg/kg

Female No.	Body	Brain		Thymus		Heart		Liver		Kidney (R)		Kidney (L)		Kidneys		Spleen	
	weight (g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F06066	264.7	1820.4	6.877	287.8	1.087	1097.7	4.147	6738.4	25.457	866.8	3.275	862.8	3.260	1729.6	6.534	513.5	1.940
F06067	255.6	1878.2	7.348	213.3	0.835	877.6	3.433	6397.2	25.028	852.1	3.334	844.1	3.302	1696.2	6.636	468.2	1.832
F06068	276.2	1913.5	6.928	126.4	0.458	912.8	3.305	6799.7	24.619	964.5	3.492	908.5	3.289	1873.0	6.781	601.5	2.178
Number of females	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Mean	265.5	1870.7	7.051	209.2	0.793	962.7	3.628	6645.1	25.035	894.5	3.367	871.8	3.284	1766.3	6.650	527.7	1.983
S.D.	10.3	47.0	0.258	80.8	0.317	118.2	0.454	216.9	0.419	61.1	0.112	33.1	0.022	93.9	0.124	67.8	0.177
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	TT	AW	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.
AW: Analysis by Aspin-Welch t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 30-3-2(continued). Organ weights of female rats at the end of the recovery period

SF 150/75 mg/kg

Female No.	Ovary (R)		Ovary (L)		Ovaries		Uterus		Thyroid gland		Adrenal gland (R)		Adrenal gland (L)		Adrenal glands	
	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)	(mg)	(mg/g)
F06066	25.8	0.097	30.1	0.114	55.9	0.211	411.9	1.556	15.8	0.060	24.9	0.094	25.7	0.097	50.6	0.191
F06067	30.6	0.120	35.5	0.139	66.1	0.259	442.8	1.732	17.5	0.068	32.1	0.126	36.2	0.142	68.3	0.267
F06068	51.2	0.185	48.8	0.177	100.0	0.362	1070.5	3.876	14.9	0.054	26.3	0.095	27.7	0.100	54.0	0.196
Number of females	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Mean	35.9	0.134	38.1	0.143	74.0	0.277	641.7	2.388	16.1	0.061	27.8	0.105	29.9	0.113	57.6	0.218
S.D.	13.5	0.046	9.6	0.032	23.1	0.077	371.6	1.292	1.3	0.007	3.8	0.018	5.6	0.025	9.4	0.043
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS
Statistical method	TT	TT	TT	TT	TT	TT	AW	AW	TT	TT	TT	TT	TT	TT	TT	TT

Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
TT: Analysis by Student's t-test.
AW: Analysis by Aspin-Welch t-test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 31-1. Macroscopic findings of male rats at the end of the dosing period

Findings	Group	Control (Vehicle)							SF 15 mg/kg												SF 50 mg/kg												SF 150/75 mg/kg						
	Animal No.	M01	M01	M01	M01	M01	M01	M01	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M04	M04	M04	M04	M04	M04	M04
		001	002	003	004	005	006	007	013	014	015	016	017	018	019	020	021	022	023	024	025	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	046
	Fate																																						D
Epididymis																																							
Nodule, yellowish white, caudal, unilateral		-	P	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Glandular stomach																																							
Dark reddish spot, mucosa, scattered		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P
Heart																																							
Whitish spot, scattered		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P
Kidney																																							
Enlargement, bilateral		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P
Pale colored area, unilateral		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-
Whitish area, single/scattered, uni-/bilateral		-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-
Liver																																							
Discoloration, dark colored		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P
Whitish area		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Lung																																							
Discoloration, reddish		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P
Ileum																																							
Diverticulum		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Spleen																																							
Small		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P
Thymus																																							
Small		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P
Tooth																																							
Discoloration, whitish, surface, maxillary/mandibular incisor		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	P	-

Notes) - : No abnormal changes P : Non-graded change

Vehicle: water for injection

Fate : blanks, Subjected to autopsy at the end of the dosing period; D, Died during the dosing period.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 31-2. Macroscopic findings of male rats at the end of the recovery period

Findings	Group	Control (Vehicle)					SF 150/75 mg/kg				
	Animal No.	M01 008	M01 009	M01 010	M01 011	M01 012	M04 043	M04 044	M04 045	M04 047	M04 048
Tooth											
Fracture, maxillary incisor		-	-	-	-	-	-	-	-	P	-
Loss, unilateral, maxillary incisor		-	-	-	-	-	-	P	-	-	-

Notes) - : No abnormal changes P : Non-graded change

Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 32-1. Macroscopic findings of female rats at the end of the dosing period

Findings	Group	Control (Vehicle)												SF 15 mg/kg												SF 50 mg/kg												SF 150/75 mg/kg											
	Animal No.	F01	F01	F01	F01	F01	F01	F01	F01	F01	F01	F01	F01	F02	F02	F02	F02	F02	F02	F02	F02	F02	F02	F02	F02	F03	F03	F03	F03	F03	F03	F03	F03	F03	F03	F03	F03	F04	F04	F04	F04	F04	F04	F04	F04	F04	F04	F04	F04
		001	002	003	004	005	006	007	008	009	010	011	012	013	014	015	016	017	018	019	020	021	022	023	024	025	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	043	044	045	046	047	048
	Fate											NC																																			DP		
Heart																																																	
Whitish area, scattered		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-
Kidney																																																	
Discoloration, pale colored, bilateral		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-
Whitish area, scattered, bilateral		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-
Liver																																																	
Diaphragmatic nodule		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Spleen																																																	
Small		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-
Thymus																																																	
Small		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	-	-	-	-	P	-	-
Tooth																																																	
Discoloration, whitish, surface, maxillary/mandibular incisor		-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	P	-	P	-	-	-	-	-	-	-	-

Notes) - : No abnormal changes P : Non-graded change

Vehicle: water for injection

Fate : blanks, Subjected to autopsy on day 5 of lactation; NC, Not copulated; DP, Died during pregnancy.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 32-2. Macroscopic findings of female rats at the end of the dosing period, satellite group

Findings	Group	Control (Vehicle)					SF 150/75 mg/kg						
	Animal No.	F05 049	F05 050	F05 051	F05 052	F05 053	F06 059	F06 060	F06 061	F06 062	F06 063	F06 064	F06 065
	Fate							D	D	D	D		
Adrenal gland													
Discoloration, dark colored, bilateral		-	-	-	-	-	-	-	-	P	-	-	-
Enlargement, bilateral		-	-	-	-	-	-	P	-	P	-	-	-
Heart													
Whitish area, scattered		-	-	-	-	-	-	P	P	P	-	-	-
Kidney													
Discoloration, pale colored, bilateral		-	-	-	-	-	-	-	P	-	-	-	-
Liver													
Discoloration, dark colored		-	-	-	-	-	-	-	P	-	P	-	-
Spleen													
Discoloration, pale colored		-	-	-	-	-	-	-	-	P	-	-	-
Small		-	-	-	-	-	-	-	-	P	P	-	-
Thymus													
Small		-	-	-	-	-	-	-	P	-	-	-	-
Tooth													
Discoloration, whitish, surface, maxillary/mandibular incisor		-	-	-	-	-	P	-	-	-	-	P	-

Notes) - : No abnormal changes P : Non-graded change

Vehicle: water for injection

Fate : blanks, Subjected to autopsy at the end of the dosing period; D, Died during the dosing

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 32-3. Macroscopic findings of female rats at the end of the recovery period

Findings	Group	Control (Vehicle)					SF 150/75 mg/kg		
	Animal No.	F05 054	F05 055	F05 056	F05 057	F05 058	F06 066	F06 067	F06 068
Heart									
Discoloration, pale colored		-	-	-	-	-	P	-	-
Tooth									
Malocclusion		-	-	-	-	-	-	-	P

Notes) - : No abnormal changes P : Non-graded change

Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 33-1. Histopathological findings of male rats at the end of the dosing period

Group	Control (Vehicle)							SF 15 mg/kg													SF 50 mg/kg													SF 150/75 mg/kg						
Animal No.	M01	M01	M01	M01	M01	M01	M01	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M04	M04	M04	M04	M04	M04	M04
Findings / Fate	001	002	003	004	005	006	007	013	014	015	016	017	018	019	020	021	022	023	024	025	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	046
																																						D
Brain						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	
	-	-	-	-	-																											-	-	-	-	-		-
Spinal cord						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	
	-	-	-	-	-																											-	-	-	-	-		-
Pituitary gland						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	
Remnant, Rathke's pouch	-	-	P	P	-																											-	-	-	-	-		-
Submandibular gland						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	
	-	-	-	-	-																											-	-	-	-	-		-
Sublingual gland						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	
	-	-	-	-	-																											-	-	-	-	-		-
Lymph node, submandibular						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	
Tingible body macrophage, increased	-	-	-	-	-																											-	-	-	-	-		3+
Thyroid gland						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	
Ectopic thymic tissue	-	-	-	-	-																											-	-	P	-	-		-
Ultimobranchial body	-	-	-	-	-																											-	P	-	P	-		-
Parathyroid gland						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	
	-	-	-	-	-																											-	-	-	-	-		-
Thymus						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	
Atrophy	-	-	-	-	-																											-	-	-	-	-		+
Tingible body macrophage, increased	-	-	-	-	-																											-	-	-	-	-		2+
Heart						NE	NE						NE	NE	NE	NE	NE	NE	NE					NE	NE	NE	NE	NE	NE	NE	NE						NE	
Degeneration/necrosis, myocardial, diffuse, with mineralization	-	-	-	-	-			-	-	-	-	-								-	-	-	-	-								-	-	-	-	-		±
Degeneration/fibrosis, myocardial, focal	-	-	-	-	-			-	-	±	±	±								±	-	-	-	±								-	-	-	-	-		-
Trachea						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	
	-	-	-	-	-																											-	-	-	-	-		-
Lung						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	
Accumulation, foam cell, alveolus	-	±	-	-	-																											-	-	-	-	-		-
Metaplasia, osseous, focal	-	-	-	-	-																											±	-	-	-	-		-
Bronchus						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	
	-	-	-	-	-																											-	-	-	-	-		-

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection
Fate : blanks, Subjected to autopsy at the end of the dosing period; D, Died during the dosing period.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 33-1(continued). Histopathological findings of male rats at the end of the dosing period

Group	Control (Vehicle)							SF 15 mg/kg												SF 50 mg/kg												SF 150/75 mg/kg						
Animal No.	M01	M01	M01	M01	M01	M01	M01	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M02	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M03	M04	M04	M04	M04	M04	M04	M04
Findings / Fate	001	002	003	004	005	006	007	013	014	015	016	017	018	019	020	021	022	023	024	025	026	027	028	029	030	031	032	033	034	035	036	037	038	039	040	041	042	046
																																						D
Liver						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	
Fatty change, hepatocyte, periportal	-	±	-	±	±															±												-	±	-	-	±		-
Foci/area, cellular alteration, vacuolated cell	-	-	-	-	-															±												-	-	-	-	-		-
Microgranuloma	±	±	±	-	-															-												-	-	±	±	-		-
Vacuolation, cytoplasmic, centrilobular, hepatocyte	-	-	-	-	-															-												-	-	-	-	-		+
Pancreas						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	
Hyperplasia, duct	-	-	-	-	-																											±	-	-	-	-		-
Stomach						NE	NE						NE	NE	NE	NE	NE	NE	NE						NE	NE	NE	NE	NE	NE	NE						NE	
Accumulation, lymphocyte, submucosa, glandular stomach	-	-	-	-	-			-	-	-	-	-								±	+	±	-	-								±	±	-	+	-		-
Cellular infiltration, eosinophil, lamina muscularis mucosa/submucosa, glandular stomach	±	±	±	+	±			+	±	+	2+	+								2+	2+	2+	2+	2+								2+	+	+	2+	2+		2+
Dendritic-like cell, increased, limiting ridge, mucosa	-	-	-	±	-			±	-	±	+	+								+	+	+	±	2+								+	+	+	+	+		±
Duodenum						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	A
	-	-	-	-	-																											-	-	-	-	-		
Jejunum						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	A
	-	-	-	-	-																											-	-	-	-	-		
Ileum						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE		NE	NE	NE	NE	NE	NE	NE						NE	A
Diverticulum	-	-	-	-	-																			P								-	-	-	-	-		
Cecum						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	
	-	-	-	-	-																											-	-	-	-	-		-
Colon						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	
	-	-	-	-	-																											-	-	-	-	-		-
Rectum						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	
	-	-	-	-	-																											-	-	-	-	-		-
Lymph node, mesenteric						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	
Tingible body macrophage, increased	-	-	-	-	-																											-	-	-	-	-		2+
Spleen						NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE						NE	
Atrophy, white pulp	-	-	-	-	-																											-	-	-	-	-		+
Deposit, pigment, brown	2+	2+	2+	2+	2+																											2+	2+	2+	2+	2+		2+
Hematopoiesis, extramedullary	+	2+	2+	±	2+																											±	+	±	±	±		+

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection
Fate : blanks, Subjected to autopsy at the end of the dosing period; D, Died during the dosing period.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 33-1(continued). Histopathological findings of male rats at the end of the dosing period

Group	Control (Vehicle)						
Animal No.	M01 001	M01 002	M01 003	M01 004	M01 005	M01 006	M01 007
Findings / Fate							
Kidney						NE	NE
Basophilic collecting duct, anisonucleosis/atypia, nuclear/mitosis	-	-	-	-	-		
Basophilic tubule, cortex	±	±	±	±	-		
Cellular infiltration, lymphocyte, interstitial	-	-	-	-	-		
Cyst, medulla	-	P	-	-	-		
Degeneration/necrosis, renal tubule, with mineralization	-	-	-	-	-		
Dilatation, lumen, distal tubule	-	-	-	-	-		
Mineralization, cortex	-	-	-	-	-		
Nephroblastoma	-	-	-	-	-		
Urinary bladder						NE	NE
	-	-	-	-	-		
Adrenal gland						NE	NE
Hypertrophy, zona fasciculata	-	-	-	-	-		
Vacuolation, cytoplasmic, zona fasciculata	-	-	-	-	±		
Testis						NE	NE
	-	-	-	-	-		
Epididymis						NE	NE
Granuloma, spermatic, unilateral	-	P	-	-	-		
Prostate						NE	NE
Cellular infiltration, lymphocyte, interstitial	-	-	±	±	-		
Seminal vesicle						NE	NE
	-	-	-	-	-		
Coagulating gland						NE	NE
	-	-	-	-	-		
Eyeball						NE	NE
	-	-	-	-	-		
Harderian gland						NE	NE
Hyperpigmentation	-	-	-	-	-		
Sciatic nerve						NE	NE
	-	-	-	-	-		
Skeletal muscle						NE	NE
	-	-	-	-	-		
Femur						NE	NE
Deposit, basophilic substance, epiphysis/growth plate/metaphysis	-	-	-	-	-		
Marrow, femur						NE	NE
	-	-	-	-	-		

Group	SF 15 mg/kg											
Animal No.	M02 013	M02 014	M02 015	M02 016	M02 017	M02 018	M02 019	M02 020	M02 021	M02 022	M02 023	M02 024
Findings / Fate												
Kidney						NE	NE	NE	NE	NE	NE	NE
Basophilic collecting duct, anisonucleosis/atypia, nuclear/mitosis	-	-	-	-	-							
Basophilic tubule, cortex	-	-	-	±	±							
Cellular infiltration, lymphocyte, interstitial	-	-	-	-	±							
Cyst, medulla	-	P	-	-	-							
Degeneration/necrosis, renal tubule, with mineralization	-	-	-	-	-							
Dilatation, lumen, distal tubule	-	-	-	-	-							
Mineralization, cortex	-	-	-	-	-							
Nephroblastoma	-	-	-	-	-							
Urinary bladder	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Adrenal gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Hypertrophy, zona fasciculata												
Vacuolation, cytoplasmic, zona fasciculata												
Testis	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Epididymis	NE	NE	NE	NE	NE	NE		NE	NE	NE	NE	NE
Granuloma, spermatic, unilateral							P					
Prostate	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cellular infiltration, lymphocyte, interstitial												
Seminal vesicle	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Coagulating gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Eyeball	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Harderian gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Hyperpigmentation												
Sciatic nerve	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Skeletal muscle	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Femur						NE	NE	NE	NE	NE	NE	NE
Deposit, basophilic substance, epiphysis/growth plate/metaphysis	-	-	-	-	-							
Marrow, femur	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Group	SF 50 mg/kg											
Animal No.	M03 025	M03 026	M03 027	M03 028	M03 029	M03 030	M03 031	M03 032	M03 033	M03 034	M03 035	M03 036
Findings / Fate												
Kidney						NE	NE	NE	NE	NE	NE	NE
Basophilic collecting duct, anisonucleosis/atypia, nuclear/mitosis	-	-	-	-	-							
Basophilic tubule, cortex	-	±	-	±	±							
Cellular infiltration, lymphocyte, interstitial	-	-	-	±	-							
Cyst, medulla	-	-	-	-	-							
Degeneration/necrosis, renal tubule, with mineralization	-	-	-	-	-							
Dilatation, lumen, distal tubule	-	-	-	-	-							
Mineralization, cortex	-	-	-	-	-							
Nephroblastoma	-	-	-	-	-							
Urinary bladder	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Adrenal gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Hypertrophy, zona fasciculata												
Vacuolation, cytoplasmic, zona fasciculata												
Testis	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Epididymis	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Granuloma, spermatic, unilateral												
Prostate	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cellular infiltration, lymphocyte, interstitial												
Seminal vesicle	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Coagulating gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Eyeball	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Harderian gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Hyperpigmentation												
Sciatic nerve	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Skeletal muscle	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Femur						NE	NE	NE	NE	NE	NE	NE
Deposit, basophilic substance, epiphysis/growth plate/metaphysis	-	-	-	-	-							
Marrow, femur	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Group	SF 150/75 mg/kg						
Animal No.	M04 037	M04 038	M04 039	M04 040	M04 041	M04 042	M04 046
Findings / Fate							D
Kidney							
Basophilic collecting duct, anisonucleosis/atypia, nuclear/mitosis	-	-	-	-	-	-	2+
Basophilic tubule, cortex	+	±	±	-	-	±	-
Cellular infiltration, lymphocyte, interstitial	+	±	-	-	-	-	-
Cyst, medulla	-	-	-	-	-	-	-
Degeneration/necrosis, renal tubule, with mineralization	-	-	-	-	-	-	+
Dilatation, lumen, distal tubule	-	-	-	-	-	±	+
Mineralization, cortex	±	±	±	-	-	-	-
Nephroblastoma	-	-	-	-	P	-	-
Urinary bladder						NE	
	-	-	-	-	-		-
Adrenal gland						NE	
Hypertrophy, zona fasciculata	-	-	-	-	-		±
Vacuolation, cytoplasmic, zona fasciculata	-	-	-	-	-		-
Testis						NE	
	-	-	-	-	-		-
Epididymis						NE	
Granuloma, spermatic, unilateral	-	-	-	-	-		-
Prostate						NE	
Cellular infiltration, lymphocyte, interstitial	-	-	-	±	±		-
Seminal vesicle						NE	
	-	-	-	-	-		-
Coagulating gland						NE	
	-	-	-	-	-		-
Eyeball						NE	
	-	-	-	-	-		-
Harderian gland						NE	
Hyperpigmentation	-	-	-	-	-		2+
Sciatic nerve						NE	
	-	-	-	-	-		-
Skeletal muscle						NE	
	-	-	-	-	-		-
Femur						NE	
Deposit, basophilic substance, epiphysis/growth plate/metaphysis	2+	2+	2+	2+	2+		2+
Marrow, femur						NE	
	-	-	-	-	-		-

Notes) - : No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection
Fate : blanks, Subjected to autopsy at the end of the dosing period; D, Died during the dosing period.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 33-2. Histopathological findings of male rats at the recovery period

Findings	Group	Control (Vehicle)					SF 150/75 mg/kg				
	Animal No.	M01 008	M01 009	M01 010	M01 011	M01 012	M04 043	M04 044	M04 045	M04 047	M04 048
Brain		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spinal cord		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Pituitary gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Submandibular gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sublingual gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, submandibular		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thyroid gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Parathyroid gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thymus		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Heart											
Degeneration/fibrosis, myocardial, focal		-	±	-	-	-	±	-	-	-	±
Trachea		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lung		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Bronchus		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 33-2(continued). Histopathological findings of male rats at the recovery period

Group	Control (Vehicle)					SF 150/75 mg/kg				
Findings / Animal No.	M01 008	M01 009	M01 010	M01 011	M01 012	M04 043	M04 044	M04 045	M04 047	M04 048
Liver	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Pancreas	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Stomach										
Accumulation, lymphocyte, submucosa, glandular stomach	-	-	-	-	-	-	-	-	-	±
Cellular infiltration, eosinophil, lamina muscularis mucosa/submucosa, glandular stomach	±	±	±	±	+	±	±	±	±	±
Dendritic-like cell, increased, limiting ridge, mucosa	-	-	-	-	+	±	+	±	-	±
Duodenum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Jejunum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Ileum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cecum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Colon	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Rectum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, mesenteric	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spleen	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 33-2(continued). Histopathological findings of male rats at the recovery period

Findings	Group	Control (Vehicle)					SF 150/75 mg/kg				
	Animal No.	M01 008	M01 009	M01 010	M01 011	M01 012	M04 043	M04 044	M04 045	M04 047	M04 048
Kidney											
Basophilic tubule, cortex		±	±	-	±	-	±	±	±	-	±
Cellular infiltration, lymphocyte, interstitial		-	-	-	-	-	-	+	-	-	±
Urinary bladder		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Adrenal gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Testis		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Epididymis		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Prostate		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Seminal vesicle		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Coagulating gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Eyeball		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Harderian gland		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sciatic nerve		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Skeletal muscle		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Femur		-	-	-	-	-	-	-	-	-	-
Marrow, femur		NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 34-1. Histopathological findings of female rats at the end of the dosing period

Group	Control (Vehicle)											
Animal No.	F01 001	F01 002	F01 003	F01 004	F01 005	F01 006	F01 007	F01 008	F01 009	F01 010	F01 011	F01 012
Fate											NC	
Brain	NE	NE					NE	NE	NE		NE	NE
			-	-	-	-				-		
Spinal cord	NE	NE					NE	NE	NE		NE	NE
			-	-	-	-				-		
Pituitary gland	NE	NE					NE	NE	NE		NE	NE
Remnant, Rathke's pouch			-	-	-	-				-		
Submandibular gland	NE	NE					NE	NE	NE		NE	NE
			-	-	-	-				-		
Sublingual gland	NE	NE					NE	NE	NE		NE	NE
Atrophy, acinus, unilateral			-	-	-	-				-		
Cellular infiltration, mononuclear cell, interstitial, unilateral			-	-	-	-				-		
Lymph node, submandibular	NE	NE					NE	NE	NE		NE	NE
			-	-	-	-				-		
Thyroid gland	NE	NE					NE	NE	NE		NE	NE
Ultimobranchial body			-	-	P	P				-		
Parathyroid gland	NE	NE					NE	NE	NE		NE	NE
			-	-	-	-				-		
Thymus	NE	NE					NE	NE	NE		NE	NE
Atrophy			-	-	-	-				-		
Heart	NE	NE					NE	NE	NE		NE	NE
Degeneration/necrosis, myocardial, diffuse, with mineralization			-	-	-	-				-		
Edema, around an artery			-	-	-	-				-		
Trachea	NE	NE					NE	NE	NE		NE	NE
			-	-	-	-				-		
Lung	NE	NE					NE	NE	NE		NE	NE
			-	-	-	-				-		
Bronchus	NE	NE					NE	NE	NE		NE	NE
			-	-	-	-				-		

Group	SF 15 mg/kg											
Animal No.	F02 013	F02 014	F02 015	F02 016	F02 017	F02 018	F02 019	F02 020	F02 021	F02 022	F02 023	F02 024
Fate												
Brain	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spinal cord	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Pituitary gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Remnant, Rathke's pouch												
Submandibular gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sublingual gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Atrophy, acinus, unilateral												
Cellular infiltration, mononuclear cell, interstitial, unilateral												
Lymph node, submandibular	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thyroid gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Ultimobranchial body												
Parathyroid gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thymus	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Atrophy												
Heart						NE	NE	NE	NE	NE	NE	NE
Degeneration/necrosis, myocardial, diffuse, with mineralization	-	-	-	-	-							
Edema, around an artery	-	-	-	-	-							
Trachea	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lung	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Bronchus	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Group	SF 50 mg/kg											
Animal No.	F03 025	F03 026	F03 027	F03 028	F03 029	F03 030	F03 031	F03 032	F03 033	F03 034	F03 035	F03 036
Fate												
Brain	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Spinal cord	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Pituitary gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Remnant, Rathke's pouch												
Submandibular gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sublingual gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Atrophy, acinus, unilateral												
Cellular infiltration, mononuclear cell, interstitial, unilateral												
Lymph node, submandibular	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thyroid gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Ultimobranchial body												
Parathyroid gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Thymus	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Atrophy												
Heart			NE	NE	NE		NE	NE		NE	NE	
Degeneration/necrosis, myocardial, diffuse, with mineralization	-	-				-			-			-
Edema, around an artery	-	-				-			-			-
Trachea	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lung	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Bronchus	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE

Group	SF 150/75 mg/kg											
Animal No.	F04 037	F04 038	F04 039	F04 040	F04 041	F04 042	F04 043	F04 044	F04 045	F04 046	F04 047	F04 048
Fate										DP		
Brain			NE			NE	NE	NE	NE			NE
	-	-		-	-					-	-	
Spinal cord			NE			NE	NE	NE	NE			NE
	-	-		-	-					-	-	
Pituitary gland			NE			NE	NE	NE	NE			NE
Remnant, Rathke's pouch	-	-		P	-					-	-	
Submandibular gland			NE			NE	NE	NE	NE			NE
	-	-		-	-					-	-	
Sublingual gland			NE			NE	NE	NE	NE			NE
Atrophy, acinus, unilateral	-	-		-	2+					-	-	
Cellular infiltration, mononuclear cell, interstitial, unilateral	-	-		-	+					-	-	
Lymph node, submandibular			NE			NE	NE	NE	NE			NE
	-	-		-	-					-	-	
Thyroid gland			NE			NE	NE	NE	NE			NE
Ultimobranchial body	P	-		-	P					-	-	
Parathyroid gland			NE			NE	NE	NE	NE			NE
	-	-		-	-					-	-	
Thymus			NE			NE	NE	NE	NE			NE
Atrophy	-	-		2+	-					+	-	
Heart			NE			NE	NE	NE	NE			NE
Degeneration/necrosis, myocardial, diffuse, with mineralization	-	-		-	-					2+	-	
Edema, around an artery	-	-		+	-					-	-	
Trachea			NE			NE	NE	NE	NE			NE
	-	-		-	-					-	-	
Lung			NE			NE	NE	NE	NE			NE
	-	-		-	-					-	-	
Bronchus			NE			NE	NE	NE	NE			NE
	-	-		-	-					-	-	

Notes) - : No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection
Fate : blanks, Subjected to autopsy on day 5 of lactation; NC, Not copulated; DP, Died during pregnancy.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 34-1(continued). Histopathological findings of female rats at the end of the dosing period

Group	Control (Vehicle)											
Animal No.	F01 001	F01 002	F01 003	F01 004	F01 005	F01 006	F01 007	F01 008	F01 009	F01 010	F01 011	F01 012
Fate											NC	
Liver	NE	NE					NE	NE	NE		NE	NE
Change, basophilic, hepatocyte			-	-	-	-				-		
Fatty change, hepatocyte, periportal			-	-	-	-				±		
Hematopoiesis, extramedullary			-	-	-	±				-		
Necrosis, focal			-	-	-	-				-		
Nodule, hepatodiaphragmatic, focal hemorrhage			-	-	-	-				-		
Pancreas	NE	NE					NE	NE	NE		NE	NE
			-	-	-	-				-		
Stomach	NE	NE					NE	NE	NE		NE	NE
Accumulation, lymphocyte, submucosa, glandular stomach			-	-	-	-				-		
Cellular infiltration, eosinophil, lamina muscularis mucosa/submucosa, glandular stomach			±	±	-	-				±		
Dendritic-like cell, increased, limiting ridge, mucosa			-	-	-	-				-		
Duodenum	NE	NE					NE	NE	NE		NE	NE
			-	-	-	-				-		
Jejunum	NE	NE					NE	NE	NE		NE	NE
			-	-	-	-				-		
Ileum	NE	NE					NE	NE	NE		NE	NE
			-	-	-	-				-		
Cecum	NE	NE					NE	NE	NE		NE	NE
			-	-	-	-				-		
Colon	NE	NE					NE	NE	NE		NE	NE
			-	-	-	-				-		
Rectum	NE	NE					NE	NE	NE		NE	NE
			-	-	-	-				-		
Lymph node, mesenteric	NE	NE					NE	NE	NE		NE	NE
Atrophy			-	-	-	-				-		
Spleen	NE	NE					NE	NE	NE		NE	NE
Atrophy, white pulp			-	-	-	-				-		
Deposit, pigment, brown			2+	2+	2+	3+				2+		
Hematopoiesis, extramedullary			2+	2+	2+	+				2+		

Group	SF 15 mg/kg											
Animal No.	F02 013	F02 014	F02 015	F02 016	F02 017	F02 018	F02 019	F02 020	F02 021	F02 022	F02 023	F02 024
Fate												
Liver	NE	NE	NE	NE	NE	NE	NE	NE		NE	NE	NE
Change, basophilic, hepatocyte									-			
Fatty change, hepatocyte, periportal									+			
Hematopoiesis, extramedullary									-			
Necrosis, focal									-			
Nodule, hepatodiaphragmatic, focal hemorrhage									P			
Pancreas	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Stomach						NE	NE	NE	NE	NE	NE	NE
Accumulation, lymphocyte, submucosa, glandular stomach	-	-	-	-	-							
Cellular infiltration, eosinophil, lamina muscularis mucosa/submucosa, glandular stomach	±	±	±	+	±							
Dendritic-like cell, increased, limiting ridge, mucosa	+	-	-	+	+							
Duodenum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Jejunum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Ileum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cecum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Colon	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Rectum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, mesenteric	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Atrophy												
Spleen	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Atrophy, white pulp												
Deposit, pigment, brown												
Hematopoiesis, extramedullary												

Group	SF 50 mg/kg											
Animal No.	F03 025	F03 026	F03 027	F03 028	F03 029	F03 030	F03 031	F03 032	F03 033	F03 034	F03 035	F03 036
Fate												
Liver	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Change, basophilic, hepatocyte												
Fatty change, hepatocyte, periportal												
Hematopoiesis, extramedullary												
Necrosis, focal												
Nodule, hepatodiaphragmatic, focal hemorrhage												
Pancreas	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Stomach			NE	NE	NE		NE	NE		NE	NE	
Accumulation, lymphocyte, submucosa, glandular stomach	-	-				-			-			-
Cellular infiltration, eosinophil, lamina muscularis mucosa/submucosa, glandular stomach	2+	±				+			+			+
Dendritic-like cell, increased, limiting ridge, mucosa	2+	+				+			+			+
Duodenum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Jejunum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Ileum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Cecum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Colon	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Rectum	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, mesenteric	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Atrophy												
Spleen	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Atrophy, white pulp												
Deposit, pigment, brown												
Hematopoiesis, extramedullary												

Group	SF 150/75 mg/kg											
Animal No.	F04 037	F04 038	F04 039	F04 040	F04 041	F04 042	F04 043	F04 044	F04 045	F04 046	F04 047	F04 048
Fate										DP		
Liver			NE			NE	NE	NE	NE			NE
Change, basophilic, hepatocyte	-	-		-	-					+	-	
Fatty change, hepatocyte, periportal	-	-		-	±					-	-	
Hematopoiesis, extramedullary	-	-		-	-					-	-	
Necrosis, focal	-	-		-	-					-	±	
Nodule, hepatodiaphragmatic, focal hemorrhage	-	-		-	-					-	-	
Pancreas			NE			NE	NE	NE	NE			NE
	-	-		-	-					-	-	
Stomach			NE			NE	NE	NE	NE			NE
Accumulation, lymphocyte, submucosa, glandular stomach	-	±		-	-					-	-	
Cellular infiltration, eosinophil, lamina muscularis mucosa/submucosa, glandular stomach	2+	2+		±	+					±	+	
Dendritic-like cell, increased, limiting ridge, mucosa	-	+		-	2+					-	2+	
Duodenum			NE			NE	NE	NE	NE	A		NE
	-	-		-	-						-	
Jejunum			NE			NE	NE	NE	NE	A		NE
	-	-		-	-						-	
Ileum			NE			NE	NE	NE	NE	A		NE
	-	-		-	-						-	
Cecum			NE			NE	NE	NE	NE	A		NE
	-	-		-	-						-	
Colon			NE			NE	NE	NE	NE			NE
	-	-		-	-					-	-	
Rectum			NE			NE	NE	NE	NE			NE
	-	-		-	-					-	-	
Lymph node, mesenteric			NE			NE	NE	NE	NE			NE
Atrophy	-	-		-	-					±	-	
Spleen			NE			NE	NE	NE	NE			NE
Atrophy, white pulp	-	-		-	-					+	-	
Deposit, pigment, brown	2+	2+		2+	2+					2+	2+	
Hematopoiesis, extramedullary	2+	2+		+	2+					±	2+	

Notes) - : No abnormal changes ±: Very slight +: Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection
Fate : blanks, Subjected to autopsy on day 5 of lactation; NC, Not copulated; DP, Died during pregnancy.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 34-1(continued). Histopathological findings of female rats at the end of the dosing period

Group	Control (Vehicle)											
Animal No.	F01 001	F01 002	F01 003	F01 004	F01 005	F01 006	F01 007	F01 008	F01 009	F01 010	F01 011	F01 012
Findings / Fate											NC	
Kidney	NE	NE					NE	NE	NE		NE	NE
Basophilic collecting duct, anisonucleosis/atypia, nuclear/mitosis			-	-	-	-				-		
Basophilic proximal tubule, straight			-	-	-	-				-		
Basophilic tubule, cortex			-	-	±	-				-		
Degeneration, vacuolar, proximal tubule, convoluted			-	-	-	-				-		
Degeneration/necrosis, renal tubule, with mineralization			-	-	-	-				-		
Dilatation, lumen, distal tubule			-	-	-	-				-		
Mineralization, cortico-medullary junction/medulla			-	-	-	-				-		
Urinary bladder	NE	NE					NE	NE	NE		NE	NE
			-	-	-	-				-		
Adrenal gland	NE	NE					NE	NE	NE		NE	NE
Hypertrophy, zona fasciculata			-	-	-	-				-		
Ovary	NE	NE					NE	NE	NE		NE	NE
			-	-	-	-				-		
Uterus	NE	NE					NE	NE	NE		NE	NE
			-	-	-	-				-		
Vagina	NE	NE					NE	NE	NE		NE	NE
Mucification, epithelium			-	-	-	-				-		
Eyeball	NE	NE					NE	NE	NE		NE	NE
			-	-	-	-				-		
Harderian gland	NE	NE					NE	NE	NE		NE	NE
			-	-	-	-				-		
Sciatic nerve	NE	NE					NE	NE	NE		NE	NE
			-	-	-	-				-		
Skeletal muscle	NE	NE					NE	NE	NE		NE	NE
			-	-	-	-				-		
Femur	NE	NE					NE	NE	NE		NE	NE
Deposit, basophilic substance, epiphysis/growth plate/metaphysis			-	-	-	-				-		
Marrow, femur	NE	NE					NE	NE	NE		NE	NE
Hematopoiesis, increased			-	-	-	±				-		

Group	SF 15 mg/kg											
Animal No.	F02 013	F02 014	F02 015	F02 016	F02 017	F02 018	F02 019	F02 020	F02 021	F02 022	F02 023	F02 024
Findings / Fate												
Kidney						NE	NE	NE	NE	NE	NE	NE
Basophilic collecting duct, anisonucleosis/atypia, nuclear/mitosis	-	-	-	-	-							
Basophilic proximal tubule, straight	-	-	-	-	-							
Basophilic tubule, cortex	±	-	±	-	-							
Degeneration, vacuolar, proximal tubule, convoluted	-	-	-	-	-							
Degeneration/necrosis, renal tubule, with mineralization	-	-	-	-	-							
Dilatation, lumen, distal tubule	-	-	-	-	-							
Mineralization, cortico-medullary junction/medulla	-	-	±	-	-							
Urinary bladder	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Adrenal gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Hypertrophy, zona fasciculata												
Ovary	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Uterus	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Vagina	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Mucification, epithelium												
Eyeball	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Harderian gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sciatic nerve	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Skeletal muscle	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Femur						NE	NE	NE	NE	NE	NE	NE
Deposit, basophilic substance, epiphysis/growth plate/metaphysis	-	-	-	-	-							
Marrow, femur	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Hematopoiesis, increased												

Group	SF 50 mg/kg											
Animal No.	F03 025	F03 026	F03 027	F03 028	F03 029	F03 030	F03 031	F03 032	F03 033	F03 034	F03 035	F03 036
Findings / Fate												
Kidney			NE	NE	NE		NE	NE		NE	NE	
Basophilic collecting duct, anisonucleosis/atypia, nuclear/mitosis	-	-				-			-		-	
Basophilic proximal tubule, straight	-	-				±			-		-	
Basophilic tubule, cortex	-	-				-			±		±	
Degeneration, vacuolar, proximal tubule, convoluted	-	-				-			-		-	
Degeneration/necrosis, renal tubule, with mineralization	-	-				-			-		-	
Dilatation, lumen, distal tubule	-	-				-			-		-	
Mineralization, cortico-medullary junction/medulla	-	-				±			-		-	
Urinary bladder	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Adrenal gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Hypertrophy, zona fasciculata												
Ovary	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Uterus	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Vagina	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Mucification, epithelium												
Eyeball	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Harderian gland	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Sciatic nerve	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Skeletal muscle	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Femur			NE	NE	NE		NE	NE		NE	NE	
Deposit, basophilic substance, epiphysis/growth plate/metaphysis	-	-				-			-		-	
Marrow, femur	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE	NE
Hematopoiesis, increased												

Group	SF 150/75 mg/kg											
Animal No.	F04 037	F04 038	F04 039	F04 040	F04 041	F04 042	F04 043	F04 044	F04 045	F04 046	F04 047	F04 048
Findings / Fate										DP		
Kidney			NE			NE	NE	NE	NE			NE
Basophilic collecting duct, anisonucleosis/atypia, nuclear/mitosis	-	-		-	-					2+	-	
Basophilic proximal tubule, straight	-	-		-	-					-	-	
Basophilic tubule, cortex	-	-		2+	±					-	-	
Degeneration, vacuolar, proximal tubule, convoluted	-	-		-	-					+	-	
Degeneration/necrosis, renal tubule, with mineralization	-	-		+	-					±	-	
Dilatation, lumen, distal tubule	-	-		±	-					-	-	
Mineralization, cortico-medullary junction/medulla	-	-		-	-					-	±	
Urinary bladder			NE			NE	NE	NE	NE			NE
	-	-		-	-					-	-	
Adrenal gland			NE			NE	NE	NE	NE			NE
Hypertrophy, zona fasciculata	-	-		-	-					±	-	
Ovary			NE			NE	NE	NE	NE			NE
	-	-		-	-					-	-	
Uterus			NE			NE	NE	NE	NE			NE
	-	-		-	-					-	-	
Vagina			NE			NE	NE	NE	NE			NE
Mucification, epithelium	-	-		-	-					+	-	
Eyeball			NE			NE	NE	NE	NE			NE
	-	-		-	-					-	-	
Harderian gland			NE			NE	NE	NE	NE			NE
	-	-		-	-					-	-	
Sciatic nerve			NE			NE	NE	NE	NE			NE
	-	-		-	-					-	-	
Skeletal muscle			NE			NE	NE	NE	NE			NE
	-	-		-	-					-	-	
Femur			NE			NE	NE	NE	NE			NE
Deposit, basophilic substance, epiphysis/growth plate/metaphysis	2+	2+		2+	2+					-	±	
Marrow, femur			NE			NE	NE	NE	NE			NE
Hematopoiesis, increased	-	-		-	-					-	-	

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection
Fate : blanks, Subjected to autopsy on day 5 of lactation; NC, Not copulated; DP, Died during pregnancy.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 34-2. Histopathological findings of female rats at the end of the dosing period, satellite group

Findings	Group	Control (Vehicle)					SF 150/75 mg/kg						
	Animal No.	F05 049	F05 050	F05 051	F05 052	F05 053	F06 059	F06 060	F06 061	F06 062	F06 063	F06 064	F06 065
	Fate							D	D	D	D		
Brain		-	-	-	-	-	-	-	-	-	-	-	-
Spinal cord		-	-	-	-	-	-	-	-	-	-	-	-
Pituitary gland		-	-	-	-	-	-	-	-	-	-	-	-
Submandibular gland		-	-	-	-	-	-	-	-	-	-	-	-
Sublingual gland		-	-	-	-	-	-	-	-	-	-	-	-
Lymph node, submandibular													
Atrophy		-	-	-	-	-	-	±	-	-	-	-	-
Tingible body macrophage, increased		-	-	-	-	-	-	-	-	2+	+	-	-
Thyroid gland													
Ectopic thymic tissue		-	-	-	-	-	P	-	-	-	-	-	-
Ultimobranchial body		P	-	-	-	-	-	-	-	-	P	-	-
Parathyroid gland		-	-	M	-	-	-	-	-	-	-	-	-
Thymus													
Atrophy		-	-	-	-	-	-	+	2+	-	-	-	-
Tingible body macrophage, increased		±	-	-	-	-	2+	-	-	-	-	-	±
Heart													
Degeneration/necrosis, myocardial, diffuse, with mineralization		-	-	-	-	-	-	2+	2+	3+	±	-	-
Trachea		-	-	-	-	-	-	-	-	-	-	-	-
Lung													
Accumulation, foam cell, alveolus		-	-	-	-	-	-	-	-	-	-	±	-
Cellular infiltration, neutrophil, alveolar wall		-	-	-	-	-	-	±	-	-	-	-	-
Metaplasia, osseous, focal		-	-	-	-	-	-	-	-	-	±	-	-
Thrombus, arteriole, focal		-	-	-	-	-	-	±	-	-	±	-	-
Bronchus		-	-	-	-	-	-	-	-	-	-	-	-

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection
Fate : blanks, Subjected to autopsy at the end of the dosing period; D, Died during the dosing period.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 34-2(continued). Histopathological findings of female rats at the end of the dosing period, satellite group

Findings	Group	Control (Vehicle)					SF 150/75 mg/kg						
	Animal No.	F05 049	F05 050	F05 051	F05 052	F05 053	F06 059	F06 060	F06 061	F06 062	F06 063	F06 064	F06 065
	Fate							D	D	D	D		
Liver													
Change, basophilic, hepatocyte		-	-	-	-	-	-	±	±	±	±	-	-
Fatty change, hepatocyte, periportal		-	-	-	-	-	±	-	-	-	-	-	-
Microgranuloma		±	±	-	-	±	±	-	-	-	-	-	-
Necrosis, focal/multifocal		-	-	±	-	-	-	-	-	-	2+	-	-
Pancreas													
		-	-	-	-	-	-	-	-	-	-	-	-
Stomach													
Cellular infiltration, eosinophil, lamina muscularis mucosa/submucosa, glandular stomach		+	+	±	±	±	2+	±	+	+	2+	2+	+
Degeneration/necrosis, submucosa/smooth muscle, with mineralization		-	-	-	-	-	-	-	2+	2+	-	-	-
Dendritic-like cell, increased, limiting ridge, mucosa		-	-	-	±	-	+	-	-	-	-	2+	+
Duodenum								A	A	A	A		
		-	-	-	-	-	-					-	-
Jejunum								A	A	A	A		
		-	-	-	-	-	-					-	-
Ileum								A	A	A	A		
		-	-	-	-	-	-					-	-
Cecum								A		A	A		
		-	-	-	-	-	-		-			-	-
Colon								A					
		-	-	-	-	-	-		-	-	-	-	-
Rectum								A	A				
		-	-	-	-	-	-			-	-	-	-
Lymph node, mesenteric													
Atrophy		-	-	-	-	-	-	±	±	-	±	-	-
Tingible body macrophage, increased		-	-	-	-	-	-	-	-	+	-	-	-
Spleen													
Atrophy, white pulp		-	-	-	-	-	-	-	2+	+	2+	-	-
Congestion, red pulp		-	-	-	-	-	-	+	2+	-	+	-	-
Deposit, pigment, brown		2+	2+	2+	2+	2+	2+	2+	+	2+	+	2+	2+
Hematopoiesis, extramedullary		±	±	±	±	±	±	±	±	±	±	±	±

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection
Fate : blanks, Subjected to autopsy at the end of the dosing period; D, Died during the dosing period.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 34-2(continued). Histopathological findings of female rats at the end of the dosing period, satellite group

Findings	Group	Control (Vehicle)					SF 150/75 mg/kg						
	Animal No.	F05 049	F05 050	F05 051	F05 052	F05 053	F06 059	F06 060	F06 061	F06 062	F06 063	F06 064	F06 065
	Fate							D	D	D	D		
Kidney													
Basophilic collecting duct, anisonucleosis/atypia, nuclear/mitosis		-	-	-	-	-	-	-	+	2+	2+	-	-
Basophilic proximal tubule, straight		-	-	-	-	-	-	2+	-	+	-	-	-
Basophilic tubule, cortex		-	±	-	-	-	±	-	-	-	-	±	-
Degeneration/necrosis, renal tubule, with mineralization		-	-	-	-	-	-	2+	+	2+	-	-	-
Urinary bladder													
		-	-	-	-	-	-	-	-	-	-	-	-
Adrenal gland													
Hypertrophy, zona fasciculata		-	-	-	-	-	-	-	±	±	-	-	-
Ovary													
Atretic follicle, increased number		-	-	-	-	-	-	-	±	-	-	-	-
Uterus													
Degeneration, vacuolar, myometrium		-	-	-	-	-	-	-	+	2+	+	-	-
Degeneration/necrosis, myometrium, with mineralization		-	-	-	-	-	-	+	-	+	+	-	-
Vagina													
		-	-	-	-	-	-	-	-	-	-	-	-
Eyeball													
		-	-	-	-	-	-	-	-	-	-	-	-
Harderian gland													
Hyperpigmentation		-	-	-	-	-	-	2+	2+	2+	2+	-	-
Sciatic nerve													
		-	-	-	-	-	-	-	-	-	-	-	-
Skeletal muscle													
		-	-	-	-	-	-	-	-	-	-	-	-
Femur													
Deposit, basophilic substance, epiphysis/growth plate/metaphysis		-	-	-	-	-	+	±	2+	+	+	+	+
Marrow, femur													
		-	-	-	-	-	-	-	-	-	-	-	-

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection
Fate : blanks, Subjected to autopsy at the end of the dosing period; D, Died during the dosing period.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 34-3. Histopathological findings of female rats at the recovery period

Findings	Group	Control (Vehicle)					SF 150/75 mg/kg		
	Animal No.	F05 054	F05 055	F05 056	F05 057	F05 058	F06 066	F06 067	F06 068
Brain		NE	NE	NE	NE	NE	NE	NE	NE
Spinal cord		NE	NE	NE	NE	NE	NE	NE	NE
Pituitary gland		NE	NE	NE	NE	NE	NE	NE	NE
Submandibular gland		NE	NE	NE	NE	NE	NE	NE	NE
Sublingual gland		NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, submandibular		NE	NE	NE	NE	NE	NE	NE	NE
Thyroid gland		NE	NE	NE	NE	NE	NE	NE	NE
Parathyroid gland		NE	NE	NE	NE	NE	NE	NE	NE
Thymus		NE	NE	NE	NE	NE	NE	NE	NE
Heart									
Fibrosis, myocardial, diffuse		-	-	-	-	-	2+	-	-
Degeneration/fibrosis, myocardial, focal		±	-	-	-	-	-	-	-
Trachea		NE	NE	NE	NE	NE	NE	NE	NE
Lung		NE	NE	NE	NE	NE	NE	NE	NE
Bronchus		NE	NE	NE	NE	NE	NE	NE	NE

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 34-3(continued). Histopathological findings of female rats at the recovery period

Findings	Group	Control (Vehicle)					SF 150/75 mg/kg		
	Animal No.	F05 054	F05 055	F05 056	F05 057	F05 058	F06 066	F06 067	F06 068
Liver		NE	NE	NE	NE	NE	NE	NE	NE
Pancreas		NE	NE	NE	NE	NE	NE	NE	NE
Stomach									
Cellular infiltration, eosinophil, lamina muscularis mucosa/submucosa, glandular stomach		+	±	±	±	±	±	±	±
Dendritic-like cell, increased, limiting ridge, mucosa		-	-	-	±	-	+	±	±
Duodenum		NE	NE	NE	NE	NE	NE	NE	NE
Jejunum		NE	NE	NE	NE	NE	NE	NE	NE
Ileum		NE	NE	NE	NE	NE	NE	NE	NE
Cecum		NE	NE	NE	NE	NE	NE	NE	NE
Colon		NE	NE	NE	NE	NE	NE	NE	NE
Rectum		NE	NE	NE	NE	NE	NE	NE	NE
Lymph node, mesenteric		NE	NE	NE	NE	NE	NE	NE	NE
Spleen		NE	NE	NE	NE	NE	NE	NE	NE

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 34-3(continued). Histopathological findings of female rats at the recovery period

Findings	Group	Control (Vehicle)					SF 150/75 mg/kg		
	Animal No.	F05 054	F05 055	F05 056	F05 057	F05 058	F06 066	F06 067	F06 068
Kidney									
Basophilic tubule, cortex		-	-	-	±	-	+	-	-
Cyst, medulla		-	-	-	-	-	P	-	-
Mineralization, cortico-medullary junction/medulla		-	-	-	-	-	+	-	±
Urinary bladder		NE	NE	NE	NE	NE	NE	NE	NE
Adrenal gland		NE	NE	NE	NE	NE	NE	NE	NE
Ovary		NE	NE	NE	NE	NE	NE	NE	NE
Uterus		NE	NE	NE	NE	NE	NE	NE	NE
Vagina		NE	NE	NE	NE	NE	NE	NE	NE
Eyeball		NE	NE	NE	NE	NE	NE	NE	NE
Harderian gland		NE	NE	NE	NE	NE	NE	NE	NE
Sciatic nerve		NE	NE	NE	NE	NE	NE	NE	NE
Skeletal muscle		NE	NE	NE	NE	NE	NE	NE	NE
Femur									
		-	-	-	-	-	-	-	-
Marrow, femur		NE	NE	NE	NE	NE	NE	NE	NE

Notes) - : No abnormal changes ±: Very slight + : Slight 2+: Moderate 3+: Marked
P : Non-graded change NE: Not examined M: Missing A: Autolysis
Vehicle: water for injection

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 35-1. Results of observations about estrous cycle

Control (vehicle: water for injection)

Animal no.	Pre-mating period						Mating period	
	Pre-treatment period			Treatment period				Times of vaginal estrus observed
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)	Stage	
F01001	D D P E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D D PL	1
F01002	D D E D D P E D D P E D D D	4-day	4.0	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1
F01003	P E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	D PL	1
F01004	D E D D P E D D P E D D P E	4-day	4.0	D D D E D D D E D D D E D D	4-day	4.0	P PL	1
F01005	D D D P E D D D P E D D P E	4/5-day	4.5	D D D P E D D D P E D D D D	5-day	5.0	PL	1
F01006	E D D D E D D D E D D D E D	4-day	4.0	D D E D D P E D D D E D D P	4-day	4.0	PL	1
F01007	D D D E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D D PL	1
F01008	D D D E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1
F01009	D D E D D P E D D P E D D P	4-day	4.0	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1
F01010	E D D D E D D P E D D P E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1
F01011	D D P E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	
F01012	D D D E D D P E D D D E D D	4-day	4.0	D E D D D E D D P E D D D E	4-day	4.0	D D P PL	1
Mean			4.0			4.1		1.0
S.D.			0.1			0.3		0.0
(N)			(12)			(12)		(11)

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 35-2. Results of observations about estrous cycle

SF (15 mg/kg)

Animal no.	Pre-mating period						Mating period	
	Pre-treatment period			Treatment period				Times of vaginal estrus observed
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)	Stage	
F02013	E D D P E D D P E D D P E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1
F02014	E D D D E D D P E D D D E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1
F02015	P E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	D PL	1
F02016	E D D P E D D P E D D P E D	4-day	4.0	D P E D D P E D D P E D D P	4-day	4.0	PL	1
F02017	D D D E D D P E E D D D E D	4/5-day	4.5	D P E D D P E D D P E D D P	4-day	4.0	PL	1
F02018	D E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	D PL	1
F02019	E E D D D E D D D E E D D D	4/5-day	4.5	E D D D E D D D P E D D P E	4/5-day	4.3	D D P PL	1
F02020	D D P E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1
F02021	D D D E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D D D D D D D D D D D D PL	1
F02022	D D E D D D E D D P E D D P	4-day	4.0	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1
F02023	D D E D D P E D D D E D D D	4-day	4.0	E D D D E D D P E D D P E D	4-day	4.0	D P PL	1
F02024	D D D E D D P E D D D E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D D PL	1
Mean			4.1			4.0		1.0
S.D.			0.2			0.1		0.0
(N)			(12)			(12)		(12)

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 35-3. Results of observations about estrous cycle

SF (50 mg/kg)

Animal no.	Pre-mating period						Mating period	
	Pre-treatment period			Treatment period				Times of vaginal estrus observed
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)	Stage	
F03025	P E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D D E D D	4-day	4.0	D PL	1
F03026	D E D D D E D D D E D D D E	4-day	4.0	D D D E D D P E D D D E D D	4-day	4.0	D PL	1
F03027	D E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E E D D D P E	5-day	5.0	D D D PL	1
F03028	D D E D D P E D D P E D D P	4-day	4.0	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1
F03029	D D E D D P E D D D E D D D	4-day	4.0	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1
F03030	D D D P E D D P E D D D P E	4/5-day	4.5	D D D D E D D D P E E D D P	irreguler	6.0	PL	1
F03031	D E D D P E D D P E D D P E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F03032	D D D E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D D PL	1
F03033	E D D P E D D P E D D P E D	4-day	4.0	D P E D D D E D D P E D D P	4-day	4.0	PL	1
F03034	P E D D D P E D D D D E D D	5-day	5.0	D P E D D D E E D D D E E D	5-day	5.0	D D PL	1
F03035	P E D D P E D D D E D D P E	4-day	4.0	D D D E D D P E D D P E D D	4-day	4.0	P PL	1
F03036	D D E D D P E D D D E D D P	4-day	4.0	E D D D E D D D P E D D D D	4/5-day	4.5	PL	1
Mean			4.1			4.4		1.0
S.D.			0.3			0.6		0.0
(N)			(12)			(12)		(12)

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 35-4. Results of observations about estrous cycle

SF (150/75 mg/kg)

Animal no.	Pre-mating period						Mating period	
	Pre-treatment period			Treatment period				Times of vaginal estrus observed
	Stage	Type	Mean length (days)	Stage	Type	Mean length (days)	Stage	
F04037	D E D D P E D D P E D D D E	4-day	4.0	D D P E D D P E D D P E D D	4-day	4.0	P PL	1
F04038	E D D P E D D P E E D D P P	4/5-day	4.5	E D D P E E D D P E E D D P	5-day	5.0	E PL	1
F04039	D D E D D P E D D P E D D P	4-day	4.0	E D D P E D D P E D D P E D	4-day	4.0	D P PL	1
F04040	P E D D P E D D P E D D D E	4-day	4.0	D D D E D D D E D D P E D D	4-day	4.0	D PL	1
F04041	E D D D P E D D D E E D D D	5-day	5.0	E E D D D P E D D D E D D D	4/5-day	4.5	P PL	1
F04042	P E D D P E D D P E D D D E	4-day	4.0	D D D E D D D E D D D E D D	4-day	4.0	P PL	1
F04043	D E E D D D E E D D D E E D	5-day	5.0	D D E D D D E E D D P E D D	4/5-day	4.5	D PL	1
F04044	D E D D P E D D P E D D P E	4-day	4.0	D D D E D D P E D D D E D D	4-day	4.0	P PL	1
F04045	D E D D D E D D D E D D D E	4-day	4.0	D D D E D D P E D D D E D D	4-day	4.0	P PL	1
F04046	D D P E D D P E D D D E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1
F04047	E D D D E D D P E E D D P E	4/5-day	4.3	E D D D E E D D P E E D D P	5-day	5.0	E PL	1
F04048	D D D E D D P E D D P E D D	4-day	4.0	P E D D P E D D P E D D P E	4-day	4.0	D D P PL	1
Mean			4.2			4.3		1.0
S.D.			0.4			0.4		0.0
(N)			(12)			(12)		(12)

D, diestrus; P, proestrus; E, estrus; PL, vaginal plug

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 36-1. Results of observations about reproductive performance

Control (vehicle: water for injection)

Male no.	Female no.	Copulation	Conception	Pairing days until copulation
M01001	F01001	+	+	4
M01002	F01002	+	+	3
M01003	F01003	+	+	2
M01004	F01004	+	+	2
M01005	F01005	+	+	1
M01006	F01006	+	+	1
M01007	F01007	+	+	4
M01008	F01008	+	+	4
M01009	F01009	+	+	3
M01010	F01010	+	+	1
M01011	F01011	+	—	
M01012	F01012	+	+	4
Total		+: 12, -: 0	+: 11, -: 1	
Mean				2.6
S.D.				1.3
(N)				(11)

+, confirmed
-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 36-2. Results of observations about reproductive performance

SF (15 mg/kg)

Male no.	Female no.	Copulation	Conception	Pairing days until copulation
M02013	F02013	+	+	1
M02014	F02014	+	+	1
M02015	F02015	+	+	2
M02016	F02016	+	+	1
M02017	F02017	+	+	1
M02018	F02018	+	+	2
M02019	F02019	+	+	4
M02020	F02020	+	+	4
M02021	F02021	+	+	14
M02022	F02022	+	+	3
M02023	F02023	+	+	3
M02024	F02024	+	+	4
Total		+: 12, -: 0	+: 12, -: 0	
Mean				3.3
S.D.				3.6
(N)				(12)

+, confirmed
-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 36-3. Results of observations about reproductive performance

SF (50 mg/kg)

Male no.	Female no.	Copulation	Conception	Pairing days until copulation
M03025	F03025	+	+	2
M03026	F03026	+	+	2
M03027	F03027	+	+	4
M03028	F03028	+	+	3
M03029	F03029	+	+	3
M03030	F03030	+	+	1
M03031	F03031	+	+	2
M03032	F03032	+	+	4
M03033	F03033	+	+	1
M03034	F03034	+	+	3
M03035	F03035	+	+	2
M03036	F03036	+	+	1
Total		+: 12, -: 0	+: 12, -: 0	
Mean				2.3
S.D.				1.1
(N)				(12)

+, confirmed
-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 36-4. Results of observations about reproductive performance

SF (150/75 mg/kg)

Male no.	Female no.	Copulation	Conception	Pairing days until copulation
M04037	F04037	+	+	2
M04038	F04038	+	+	2
M04039	F04039	+	+	3
M04040	F04040	+	+	2
M04041	F04041	+	+	2
M04042	F04042	+	+	2
M04043	F04043	+	+	2
M04044	F04044	+	+	2
M04045	F04045	+	+	2
M04037	F04046	+	Died on day 7 of pregnanacy	1
M04047	F04047	+	+	2
M04048	F04048	+	+	4
Total		+: 12, -: 0	+: 11, -: 0	
Mean				2.2
S.D.				0.7
(N)				(12)

+, confirmed
-, not confirmed

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 37-1. Observation of offspring (F_1)

Control (vehicle: water for injection)

Dam No.	Gestation length (days)	Number of corpora lutea	Number of implan-tation scars	Implan-tation index (%)	Delivery index (dams) (%)	Number of offspring at birth: Number of offspring	Live: Male	Live: Female	Live: Total	Sex ratio	Dead offspring	Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring 4 days: Male	4 days: Female	Sex ratio	Viability index (%)	External abnormalities [b] (Number)	(%)
F01001	21	16	15	93.8	+	15	11	4	15	0.73	0	100.0	100.0	100.0	11	4	0.73	100.0	0	0.0
F01002	22	16	16	100.0	+	16	11	5	16	0.69	0	100.0	100.0	100.0	11	4	0.73	93.8	0	0.0
F01003	22	15	15	100.0	+	15	8	7	15	0.53	0	100.0	100.0	100.0	7	7	0.50	93.3	0	0.0
F01004	22	14	14	100.0	+	14	6	8	14	0.43	0	100.0	100.0	100.0	5	8	0.38	92.9	0	0.0
F01005	22	16	16	100.0	+	16	6	10	16	0.38	0	100.0	100.0	100.0	6	10	0.38	100.0	0	0.0
F01006	22	15	15	100.0	+	15	7	8	15	0.47	0	100.0	100.0	100.0	7	8	0.47	100.0	0	0.0
F01007	22	15	15	100.0	+	15	7	8	15	0.47	0	100.0	100.0	100.0	7	8	0.47	100.0	0	0.0
F01008	22	16	15	93.8	+	15	5	10	15	0.33	0	100.0	100.0	100.0	5	10	0.33	100.0	0	0.0
F01009	22	14	14	100.0	+	14	8	6	14	0.57	0	100.0	100.0	100.0	7	6	0.54	92.9	0	0.0
F01010	22	15	15	100.0	+	14	6	8	14	0.43	0	93.3	93.3	100.0	6	8	0.43	100.0	0	0.0
F01012	22	13	13	100.0	+	12	4	7	11	0.36	1	92.3	84.6	91.7	4	7	0.36	100.0	0	0.0
Number of dams	11	11	11	11	11 [a]	11			11	11	11	11	11	11			11	11	11	11
Total		165	163			161	79	81	160		1				76	80			0	
Mean	21.9	15.0	14.8	98.9		14.6	7.2	7.4	14.5	0.49	0.1	98.7	98.0	99.2	6.9	7.3	0.48	97.5		0.0
S.D.	0.3	1.0	0.9	2.5		1.1	2.2	1.9	1.4	0.13	0.3	2.9	4.9	2.5	2.3	2.0	0.14	3.4		0.0
%					100.0															

+: Dams with live offspring, -: dams without live offspring.

a): Number of dams with live offspring.

b): Number of external abnormalities in live offspring at birth.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 37-2. Observation of offspring (F_1)

SF 15 mg/kg

Dam No.	Gestation length (days)	Number of corpora lutea	Number of implan-tation scars	Implan-tation index (%)	Delivery index (dams) (%)	Number of offspring at birth: Number of offspring	Live: Male	Live: Female	Live: Total	Sex ratio	Dead offspring	Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring 4 days: Male	4 days: Female	Sex ratio	Viability index (%)	External abnormalities [b] (Number)	(%)
F02013	22	18	17	94.4	+	16	7	9	16	0.44	0	94.1	94.1	100.0	7	9	0.44	100.0	0	0.0
F02014	22	17	17	100.0	+	14	8	6	14	0.57	0	82.4	82.4	100.0	8	6	0.57	100.0	0	0.0
F02015	22	16	15	93.8	+	15	8	7	15	0.53	0	100.0	100.0	100.0	8	7	0.53	100.0	0	0.0
F02016	22	16	16	100.0	+	16	7	9	16	0.44	0	100.0	100.0	100.0	7	9	0.44	100.0	0	0.0
F02017	22	16	15	93.8	+	15	4	11	15	0.27	0	100.0	100.0	100.0	4	11	0.27	100.0	0	0.0
F02018	22	18	18	100.0	+	18	9	8	17	0.53	1	100.0	94.4	94.4	9	8	0.53	100.0	0	0.0
F02019	22	15	15	100.0	+	13	3	10	13	0.23	0	86.7	86.7	100.0	3	10	0.23	100.0	0	0.0
F02020	23	15	15	100.0	+	13	4	9	13	0.31	0	86.7	86.7	100.0	4	9	0.31	100.0	0	0.0
F02021	22	14	14	100.0	+	14	7	7	14	0.50	0	100.0	100.0	100.0	7	7	0.50	100.0	0	0.0
F02022	22	18	18	100.0	+	17	5	11	16	0.31	1	94.4	88.9	94.1	4	11	0.27	93.8	0	0.0
F02023	22	16	16	100.0	+	14	7	7	14	0.50	0	87.5	87.5	100.0	7	7	0.50	100.0	0	0.0
F02024	23	15	15	100.0	+	12	9	3	12	0.75	0	80.0	80.0	100.0	9	3	0.75	100.0	0	0.0
Number of dams	12	12	12	12	12 [a]	12			12	12	12	12	12	12			12	12	12	12
Total		194	191			177	78	97	175		2				77	97			0	
Mean	22.2	16.2	15.9	98.5		14.8	6.5	8.1	14.6	0.45	0.2	92.7	91.7	99.0	6.4	8.1	0.45	99.5		0.0
S.D.	0.4	1.3	1.3	2.7		1.8	2.0	2.3	1.5	0.15	0.4	7.6	7.3	2.2	2.1	2.3	0.15	1.8		0.0
%					100.0															
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		NS
Statistical method	AN	AN	DU	KW	DU	AN	AN	AN	AN	AN	AN	KW	AN	AN	AN	AN	AN	KW		AN

Significantly different from the control group (*: P<0.05, **: P<0.01).

+: Dams with live offspring, -: dams without live offspring.

a): Number of dams with live offspring.

b): Number of external abnormalities in live offspring at birth.

NS: Not significantly different from the control group.

AN: Analysis by variance (one-way layout).

KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 37-3. Observation of offspring (F_1)

SF 50 mg/kg

Dam No.	Gestation length (days)	Number of corpora lutea	Number of implan-tation scars	Implan-tation index (%)	Delivery index (dams) (%)	Number of offspring at birth: Number of offspring	Live: Male	Live: Female	Live: Total	Sex ratio	Dead offspring	Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring: 4 days: Male	4 days: Female	Sex ratio	Viability index (%)	External abnormalities b) (Number)	(%)
F03025	22	17	14	82.4	+	14	6	8	14	0.43	0	100.0	100.0	100.0	5	8	0.38	92.9	0	0.0
F03026	22	15	15	100.0	+	13	6	7	13	0.46	0	86.7	86.7	100.0	6	7	0.46	100.0	0	0.0
F03027	22	13	13	100.0	+	13	6	7	13	0.46	0	100.0	100.0	100.0	6	7	0.46	100.0	0	0.0
F03028	22	15	15	100.0	+	15	8	7	15	0.53	0	100.0	100.0	100.0	8	6	0.57	93.3	0	0.0
F03029	22	15	15	100.0	+	15	6	9	15	0.40	0	100.0	100.0	100.0	6	9	0.40	100.0	0	0.0
F03030	22	14	14	100.0	+	13	3	10	13	0.23	0	92.9	92.9	100.0	3	10	0.23	100.0	0	0.0
F03031	22	15	15	100.0	+	15	7	8	15	0.47	0	100.0	100.0	100.0	7	8	0.47	100.0	0	0.0
F03032	22	15	15	100.0	+	15	5	10	15	0.33	0	100.0	100.0	100.0	5	10	0.33	100.0	0	0.0
F03033	22	15	13	86.7	+	12	8	4	12	0.67	0	92.3	92.3	100.0	8	4	0.67	100.0	0	0.0
F03034	22	18	16	88.9	+	15	9	5	14	0.64	1	93.8	87.5	93.3	9	5	0.64	100.0	0	0.0
F03035	22	14	14	100.0	+	14	9	5	14	0.64	0	100.0	100.0	100.0	9	5	0.64	100.0	0	0.0
F03036	22	16	15	93.8	+	14	5	9	14	0.36	0	93.3	93.3	100.0	5	9	0.36	100.0	0	0.0
Number of dams	12	12	12	12	12 a)	12			12	12	12	12	12	12			12	12	12	12
Total		182	174			168	78	89	167		1				77	88			0	
Mean	22.0	15.2	14.5	96.0		14.0	6.5	7.4	13.9	0.47	0.1	96.6	96.1	99.4	6.4	7.3	0.47	98.9		0.0
S.D.	0.0	1.3	0.9	6.4		1.0	1.8	2.0	1.0	0.13	0.3	4.6	5.2	1.9	1.8	2.0	0.14	2.7		0.0
%					100.0															
Significance	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		NS
Statistical method	AN	AN	DU	KW	DU	AN	AN	AN	AN	AN	AN	KW	AN	AN	AN	AN	AN	KW		AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
+: Dams with live offspring, -: dams without live offspring.
a): Number of dams with live offspring.
b): Number of external abnormalities in live offspring at birth.
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
DU: Analysis by Dunnett's test.
KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 37-4. Observation of offspring (F_1)

SF 150/75 mg/kg

Dam No.	Gestation length (days)	Number of corpora lutea	Number of implan-tation scars	Implan-tation index (%)	Delivery index (dams) (%)	Number of offspring at birth: Number of offspring	Live: Male	Live: Female	Live: Total	Sex ratio	Dead offspring	Delivery index (offspring) (%)	Birth index (%)	Live birth index (%)	Number of live offspring 4 days: Male	4 days: Female	Sex ratio	Viability index (%)	External abnormalities b) (Number)	(%)
F04037	22	15	15	100.0	+	15	5	10	15	0.33	0	100.0	100.0	100.0	5	10	0.33	100.0	0	0.0
F04038	21	15	15	100.0	+	15	3	12	15	0.20	0	100.0	100.0	100.0	3	12	0.20	100.0	0	0.0
F04039	22	18	18	100.0	+	17	10	7	17	0.59	0	94.4	94.4	100.0	10	7	0.59	100.0	0	0.0
F04040	22	15	15	100.0	+	14	9	5	14	0.64	0	93.3	93.3	100.0	7	4	0.64	78.6	0	0.0
F04041	22	15	15	100.0	+	13	4	8	12	0.33	1	86.7	80.0	92.3	4	8	0.33	100.0	0	0.0
F04042	22	15	15	100.0	+	14	6	8	14	0.43	0	93.3	93.3	100.0	6	8	0.43	100.0	0	0.0
F04043	23	19	19	100.0	+	18	10	8	18	0.56	0	94.7	94.7	100.0	10	8	0.56	100.0	0	0.0
F04044	22	19	18	94.7	+	17	8	8	16	0.50	1	94.4	88.9	94.1	8	8	0.50	100.0	0	0.0
F04045	22	16	16	100.0	+	16	6	10	16	0.38	0	100.0	100.0	100.0	6	10	0.38	100.0	0	0.0
F04046	Died on day 7 of pregnancy																			
F04047	21	15	15	100.0	+	14	8	6	14	0.57	0	93.3	93.3	100.0	8	6	0.57	100.0	0	0.0
F04048	22	17	16	94.1	+	16	5	11	16	0.31	0	100.0	100.0	100.0	5	11	0.31	100.0	0	0.0
Number of dams	11	11	11	11	11 a)	11			11	11	11	11	11	11			11	11	11	11
Total		179	177			169	74	93	167		2				72	92			0	
Mean	21.9	16.3	16.1	99.0		15.4	6.7	8.5	15.2	0.44	0.2	95.5	94.4	98.8	6.5	8.4	0.44	98.1		0.0
S.D.	0.5	1.7	1.5	2.3		1.6	2.4	2.1	1.7	0.14	0.4	4.2	6.1	2.8	2.3	2.3	0.14	6.5		0.0
%					100.0															
Significance	NS	NS	*	NS	*	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS	NS		NS
Statistical method	AN	AN	DU	KW	DU	AN	AN	AN	AN	AN	AN	KW	AN	AN	AN	AN	AN	KW		AN

Significantly different from the control group (*: P<0.05, **: P<0.01).
+: Dams with live offspring, -: dams without live offspring.
a): Number of dams with live offspring.
b): Number of external abnormalities in live offspring at birth.
Significantly different from control (vehicle: water for injection) (*: P<0.05).
NS: Not significantly different from the control group.
AN: Analysis by variance (one-way layout).
DU: Analysis by Dunnett's test.
KW: Analysis by Kruskal-Wallis' test (one-way layout).

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 38-1. Body weights of offspring (F_1) before weaning

Control (vehicle: water for injection)

Dam No.	Days after birth							
	Male body weight				Female body weight			
	0		4		0		4	
F01001	6.4	(11)	10.3	(11)	5.7	(4)	9.4	(4)
F01002	6.6	(11)	9.4	(11)	6.1	(5)	9.1	(4)
F01003	6.7	(8)	10.3	(7)	6.7	(7)	10.2	(7)
F01004	6.7	(6)	11.1	(5)	6.2	(8)	10.5	(8)
F01005	6.3	(6)	9.8	(6)	5.9	(10)	8.9	(10)
F01006	6.7	(7)	10.0	(7)	6.1	(8)	9.5	(8)
F01007	7.2	(7)	10.9	(7)	6.8	(8)	10.0	(8)
F01008	6.9	(5)	10.5	(5)	6.6	(10)	10.2	(10)
F01009	6.5	(8)	10.6	(7)	6.1	(6)	10.2	(6)
F01010	6.8	(6)	10.5	(6)	6.4	(8)	9.9	(8)
F01012	6.8	(4)	11.7	(4)	6.6	(7)	11.1	(7)
Number of dams	11		11		11		11	
Mean	6.7		10.5		6.3		9.9	
S.D.	0.2		0.6		0.4		0.6	

Each value shows mean per dam (g).
Figures in parentheses indicate number of offspring.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 38-2. Body weights of offspring (F_1) before weaning

SF 15 mg/kg

Dam No.	Days after birth							
	Male body weight				Female body weight			
	0		4		0		4	
F02013	7.2	(7)	11.3	(7)	6.5	(9)	10.5	(9)
F02014	6.9	(8)	11.1	(8)	6.6	(6)	10.8	(6)
F02015	6.3	(8)	10.3	(8)	5.8	(7)	9.7	(7)
F02016	7.0	(7)	10.4	(7)	6.5	(9)	9.2	(9)
F02017	5.9	(4)	9.2	(4)	5.8	(11)	9.3	(11)
F02018	5.7	(9)	9.4	(9)	5.4	(8)	8.4	(8)
F02019	7.1	(3)	11.8	(3)	6.7	(10)	11.1	(10)
F02020	8.2	(4)	13.9	(4)	6.9	(9)	11.5	(9)
F02021	6.9	(7)	11.0	(7)	6.4	(7)	10.4	(7)
F02022	6.0	(5)	10.7	(4)	5.7	(11)	9.5	(11)
F02023	7.1	(7)	10.9	(7)	6.7	(7)	10.4	(7)
F02024	7.9	(9)	12.8	(9)	7.3	(3)	11.8	(3)
Number of dams	12		12		12		12	
Mean	6.9		11.1		6.4		10.2	
S.D.	0.8		1.3		0.6		1.0	
Significance	NS		NS		NS		NS	
Statistical method	DT		DT		DT		DU	

Each value shows mean per dam (g).
Figures in parentheses indicate number of offspring.
Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
DT: Analysis by Dunnett type mean rank test.
DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 38-3. Body weights of offspring (F_1) before weaning

SF 50 mg/kg

Dam No.	Days after birth							
	Male body weight				Female body weight			
	0		4		0		4	
F03025	7.3	(6)	11.8	(5)	7.2	(8)	11.6	(8)
F03026	7.3	(6)	11.7	(6)	6.8	(7)	10.9	(7)
F03027	7.3	(6)	11.0	(6)	6.8	(7)	10.6	(7)
F03028	7.4	(8)	12.4	(8)	6.9	(7)	11.6	(6)
F03029	7.0	(6)	11.5	(6)	6.7	(9)	11.3	(9)
F03030	6.9	(3)	10.2	(3)	6.5	(10)	9.9	(10)
F03031	6.5	(7)	10.2	(7)	6.4	(8)	10.2	(8)
F03032	7.1	(5)	10.5	(5)	6.7	(10)	10.0	(10)
F03033	6.5	(8)	10.9	(8)	6.4	(4)	10.9	(4)
F03034	6.8	(9)	11.3	(9)	6.7	(5)	10.8	(5)
F03035	6.7	(9)	12.0	(9)	6.4	(5)	11.7	(5)
F03036	7.0	(5)	11.6	(5)	6.7	(9)	11.7	(9)
Number of dams	12		12		12		12	
Mean	7.0		11.3		6.7		10.9	
S.D.	0.3		0.7		0.2		0.7	
Significance	NS		NS		NS		*	
Statistical method	DT		DT		DT		DU	

Each value shows mean per dam (g).
Figures in parentheses indicate number of offspring.
Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
DT: Analysis by Dunnett type mean rank test.
DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 38-4. Body weights of offspring (F_1) before weaning

SF 150/75 mg/kg

Dam No.	Days after birth							
	Male body weight				Female body weight			
	0		4		0		4	
F04037	6.2	(5)	10.0	(5)	6.2	(10)	9.7	(10)
F04038	6.4	(3)	9.9	(3)	5.9	(12)	9.4	(12)
F04039	6.0	(10)	9.8	(10)	5.3	(7)	8.1	(7)
F04040	6.2	(9)	6.4	(7)	5.9	(5)	6.3	(4)
F04041	6.8	(4)	11.2	(4)	6.1	(8)	10.3	(8)
F04042	7.0	(6)	11.6	(6)	6.5	(8)	11.0	(8)
F04043	6.2	(10)	8.6	(10)	5.8	(8)	8.3	(8)
F04044	6.5	(8)	10.6	(8)	6.3	(8)	10.5	(8)
F04045	6.6	(6)	9.2	(6)	6.1	(10)	8.6	(10)
F04046	Died on day 7 of pregnancy							
F04047	5.9	(8)	9.7	(8)	5.7	(6)	9.2	(6)
F04048	6.6	(5)	10.9	(5)	6.1	(11)	10.0	(11)
Number of dams	11		11		11		11	
Mean	6.4		9.8		6.0		9.2	
S.D.	0.3		1.4		0.3		1.3	
Significance	NS		NS		NS		NS	
Statistical method	DT		DT		DT		DU	

Each value shows mean per dam (g).
Figures in parentheses indicate number of offspring.
Significantly different from the control group (*: P<0.05, **: P<0.01).
NS: Not significantly different from the control group.
DT: Analysis by Dunnett type mean rank test.
DU: Analysis by Dunnett's test.

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 39-1. General conditions in offspring (F_1) before weaning

Control (vehicle: water for injection)

Dam No.	Number of offspring and general conditions	Days after birth 0	1	2	3	4
F01001	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F01002	Number of offspring	16	16	16	15	15
	General appearance, No abnormality	16	16	15	15	15
	General appearance, Death	0	0	1	0	0
F01003	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	14
	General appearance, Death	0	0	0	0	1
F01004	Number of offspring	14	14	14	13	13
	General appearance, No abnormality	14	14	13	13	13
	General appearance, Death	0	0	1	0	0
F01005	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F01006	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F01007	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F01008	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F01009	Number of offspring	14	14	13	13	13
	General appearance, No abnormality	14	13	13	13	13
	General appearance, Death	0	1	0	0	0
F01010	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F01012	Number of offspring	11	11	11	11	11
	General appearance, No abnormality	11	11	11	11	11
	Number of offspring	160	160	159	157	157
	General appearance, No abnormality	160	159	157	157	156
	General appearance, Death		1	2		1

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 39-2. General conditions in offspring (F_1) before weaning

SF 15 mg/kg

Dam No.	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
F02013	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F02014	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F02015	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F02016	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F02017	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F02018	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F02019	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F02020	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F02021	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F02022	Number of offspring	16	16	15	15	15
	General appearance, No abnormality	16	15	15	15	15
	General appearance, Death	0	1	0	0	0
F02023	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F02024	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
	Number of offspring	175	175	174	174	174
	General appearance, No abnormality	175	174	174	174	174
	General appearance, Death		1			

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 39-3. General conditions in offspring (F_1) before weaning

SF 50 mg/kg

Dam No.	Number of offspring and general conditions	Days after birth				
		0	1	2	3	4
F03025	Number of offspring	14	14	13	13	13
	General appearance, No abnormality	14	12	13	13	13
	General appearance, Death	0	2	0	0	0
F03026	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F03027	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F03028	Number of offspring	15	15	14	14	14
	General appearance, No abnormality	15	14	14	14	14
	General appearance, Death	0	1	0	0	0
F03029	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F03030	Number of offspring	13	13	13	13	13
	General appearance, No abnormality	13	13	13	13	13
F03031	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F03032	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F03033	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
F03034	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F03035	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F03036	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
	Number of offspring	167	167	165	165	165
	General appearance, No abnormality	167	164	165	165	165
	General appearance, Death		3			

Combined repeat dose and reproductive/developmental toxicity screening test of sodium fluorophosphate by oral administration in rats

Appendix 39-4. General conditions in offspring (F_1) before weaning

SF 150/75 mg/kg

Dam No.	Number of offspring and general conditions	Days after birth 0	1	2	3	4
F04037	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F04038	Number of offspring	15	15	15	15	15
	General appearance, No abnormality	15	15	15	15	15
F04039	Number of offspring	17	17	17	17	17
	General appearance, No abnormality	17	17	17	17	17
F04040	Number of offspring	14	14	14	13	12
	General appearance, No abnormality	14	14	13	12	11
	General appearance, Death	0	0	1	1	1
F04041	Number of offspring	12	12	12	12	12
	General appearance, No abnormality	12	12	12	12	12
F04042	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F04043	Number of offspring	18	18	18	18	18
	General appearance, No abnormality	18	18	18	18	18
F04044	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F04045	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
F04047	Number of offspring	14	14	14	14	14
	General appearance, No abnormality	14	14	14	14	14
F04048	Number of offspring	16	16	16	16	16
	General appearance, No abnormality	16	16	16	16	16
	Number of offspring	167	167	167	166	165
	General appearance, No abnormality	167	167	166	165	164
	General appearance, Death			1	1	1

信頼性保証書

表題　　フッ化リン酸二ナトリウムのラットを用いる反復投与毒性・生殖発生毒性併合試験

試験番号　　R-12-008

この試験に関する信頼性保証部門による査察および監査状況等は下記のとおりであった。

査察・監査項目	査察・監査年月日	運営管理者および試験責任者への報告年月日
試験計画書	2012年10月15日	2012年10月15日
試験計画書変更書		
R-12-008-No.1	2012年11月29日	2012年11月29日
R-12-008-No.2	2012年12月14日	2012年12月14日
R-12-008-No.3	2013年 1月 9日	2013年 1月 9日
R-12-008-No.4	2013年 3月21日	2013年 3月21日
R-12-008-No.5	2013年 4月 1日	2013年 4月 1日
動物の受入れおよび検疫	2012年10月22日	2012年10月22日
検体調製および含量試験	2012年11月 2日	2012年11月 2日
群分け	2012年11月 4日	2012年11月 4日
体重測定、給餌量測定、投与および一般状態の観察	2012年11月 5日	2012年11月 5日
性周期観察	2012年11月 6日	2012年11月 6日
詳細な症状観察	2012年11月12日	2012年11月12日
交尾確認	2012年11月20日	2012年11月20日
尿検査	2012年12月11、12日	2012年12月13日
分娩状態および出生児の観察	2012年12月12日	2012年12月13日
機能検査	2012年12月13、16日	2012年12月16日
出生児剖検、血液学検査、血液生化学検査、雄動物剖検、器官重量測定および固定	2012年12月17日	2012年12月17日
病理組織学的検査(標本作製:切り出し)	2013年 1月30日	2013年 1月31日
報告書草案および生データ	2013年 4月15～18日	2013年 4月18日
最終報告書	2014年 2月 3日	2014年 2月 3日

試験は、「新規化学物質等に係る試験を実施する試験施設に関する基準について」(平成23年3月31日、薬食発0331第8号、平成23・03・29製局第6号、環保企発第110331010号)を遵守して実施され、また、この報告書は試験に使用された方法および手順を正確に記載し、記載された結果は試験の生データを正確に反映していることを保証する。

2014年2月3日

一般財団法人食品薬品安全センター 秦[redacted]
信頼性保証部門責任者 [redacted]