参考資料４

三酸化二アンチモンに関する OECD のリスク評価

OECDのSIAPの記述（抜粋）		OECD・SIAR（EU・Risk Assessment Report）の記述（左記関連抜粋）	備考
(Repeat-ed dose toxicity) **反復投与毒性**	The repeated dose toxicity of diantimony trioxide has been investigated in several animal studies via the inhalation and oral routes of exposure. The majority of these studies are considered inconclusive because they do not comply with current test guidelines, but those that are conclusive showed that diantimony trioxide is toxic to lung. In an inhalation repeated dose toxicity study (not following OECD test guideline), the substance was administered via whole body inhalation to 65 rats/sex/dose at 0, 0.06, 0.51 or 4.50 mg/m3, for 5 days/week for 12 months, followed by a 12-month observation period. Interstitial fibrosis, granulomatous inflammation and bronchiolar/alveolar hyperplasia occurred in a number of animals during the observation period, most pronounced in the high-dose group. Increased numbers of alveolar/intraalveolar macrophages and particulate material in alveolar/intraalveolar macrophages were seen in all dose groups during both the exposure and the observation periods. The data showed a lung burden-dependent effect on the diantimony trioxide clearance rate in the high-dose group. It was calculated that with a lung containing approximately 2 mg of diantimony trioxide after 52 weeks of exposure, pulmonary clearance was decreased by 80% with an increase in the clearance halftime from 2 to 10 months. The clearance mechanism was significantly impaired at this exposure level and was interpreted as an intrinsic toxic effect of diantimony trioxide rather than a general effect due to particle overload. Absolute and relative lung weights were unaffected in all exposure groups. Based on impaired lung clearance, the LOAEC and NOAEC for repeated dose inhalation toxicity were considered to be 4.50 mg/m3 and 0.51 mg/m3, respectively. The NOAEC was determined in a study with a high background incidence of lung inflammation in controls; therefore there is some uncertainty regarding the reliability of the numerical values. In an OECD guideline 90-day oral study, diantimony trioxide did not cause systemic toxicity at doses up to 1686 and 1879 mg/kg bw/day in male and female rats, respectively. 三酸化二アンチモン反復投与毒性試験については、いくつかの吸入ばく露、経口投与の動物実験データがある。これらの試験の多くは、現在のテストガイドラインに準拠していないので、結論づけられないと考えられるが、結論づけられるものは、三酸化二アンチモンが肺に毒性があることを示している。ある反復吸入全身ばく露試験（OECDガイドラインには準拠していない）では、三酸化二アンチモンが65匹のラットに0, 0.06, 0.51, 4.50 mg/m3,で週5日で12か月処理され、続く12ヶ月観察された。肺繊維症、肉芽腫性炎、気管支／肺胞過形成が観察期間中若干の動物で確認されており、ほとんど高用量区であった。肺胞／肺胞内マクロファージと肺胞／肺胞内マクロファージ内の粒子状物質の増加が、すべての用量区で、ばく露期間及び観察期間の両方でみられた。そのデータは高用量区の三酸化二アンチモンクリアランスレートへの肺負荷依存効果を示している。52週間の ばく露後、ほぼ2mgの三酸化二アンチモンの肺内蓄積で肺クリアランスは80%低下し、クリアランス半減期は2ヶ月から10ヶ月に増加した。この ばく露レベルでクリアランスメカニズムは有意に阻害されており、粒子負荷による一般的な影響を超えた三酸化二アンチモン固有の有害な影響と解された。肺の絶対的及び相対的重量は全ての ば	**4.1.2.6 Repeated dose toxicity** **4.1.2.6.1 Studies in animals** In a subsequent whole-body inhalation study, performed by Bio/dynamics Inc. (Newton and Daly, 1990) and published by **Newton and co-workers (1994),** the oncogenicity of diantimony trioxide was evaluated (Newton and Daly, 1990; Newton et al., 1994). This study is also reported in the 4.1.2.1 Toxicokinetics and 4.1.2.8. Carcinogenicity sections. Fisher 344 rats, 65 males and 65 females per group, 8 weeks of age, were exposed to diantimony trioxide at 0, 0.06, 0.51 or 4.50 mg/m3 for 6hr/d, 5d/wk for 12 months followed by a 12-month observation period. Control animals were exposed to clean air only. The flow rate was 18-25 complete air changes per hour (the recommended flow rate in OECD guideline 412, 413 and 453 is 12-15 air changes per hour, Rapporteur comment). Five animals per sex per group were sacrificed at 6 and 12 months of exposure and at 6 months post-exposure. All surviving animals were sacrificed at 24 months (12 months post-exposure). The purity of the diantimony trioxide was 99.68 % and the particle MMAD was 3.76±0.84 µm with a geometric standard deviation of 1.79±0.32 for all concentrations. The concentrations of diantimony trioxide were determined by atomic absorption.（中略） Table 4-48. Chronic interstitial inflammation (minimal to moderate severity) was observed in the lungs of several control and treated animals during both the exposure and the observation periods. Interstitial fibrosis, granulomatous inflammation and bronchiolar/alveolar hyperplasia (all of minimal to moderate severity) occurred in a small number of animals during the observation period and was most pronounced in the high-dose group. Increased numbers of alveolar/intraalveolar macrophages and particulate material in alveolar/intraalveolar macrophages were seen in all dose groups (but not in the control group) during both the exposure and the observation periods. However, the increase in alveolar macrophages may be regarded as a normal pulmonary response to the foreign particles entering the lung. （中略） The diantimony trioxide lung burden data show (see subsection 4.1.2.1.1) a lung burdendependent effect on the diantimony trioxide clearance rate in the high dose group. It was calculated that with a lung containing approximately 2 mg of diantimony trioxide after 52 weeks of exposure, pulmonary clearance was decreased by 80 % with an increase in the clearance halftime from 2 to 10 months. Thus, the clearance mechanism was significantly impaired at this exposure level and was interpreted by the authors as an intrinsic toxic effect of diantimony trioxide rather than a general effect due to particle overload. This was assumed since the rate of clearance from the lungs of deposited benign or slightly toxic insoluble particles has been reported to be reduced by 50 % at a dust volume of about 1000 nl/lung (Muhle et al., 1990). In the current study a 50 % inhibition of clearance was seen at 400 µg of diantimony trioxide/lung. Volumetrically, with a diantimony trioxide density of 5.5 g/cm3, this is according to Newton and coworkers (1994) equal to a dust volume of about 270 nl/lung. However, according to the rapporteur, 400 µg of diantimony trioxide is equal to about 73 nl (calculated as 400 µg / 5.5 g/cm3). （中略） A NOAEC of 0.51 mg/m3 is derived from this study based on impaired lung clearance observed at 4.50	別添dossier P50 （有害性総合評価表参照）

	く露区で影響を受けなかった。肺クリアランス阻害に基づき、反復投与毒性のLOAECとNOAECは、それぞれ4.50 mg/m3 と 0.51 mg/m3と考えられる。NOAECはコントロール区の肺の炎症の高いバックグラウンドの発生のある試験で決定されたので、数値の信頼度に関してある程度の不確実さがある。OECDガイドラインに基づく90日の経口試験で三酸化二アンチモンは、組織的な毒性を雄では1686 、雌では1879 mg/kg bw/day の用量まで引き起こさなかった。	mg/m3. Although there might be some uncertainty regarding the accuracy of the LOAEC and NOAEC numerical values, as the study had a high background incidence of lung inflammation in control animals, the NOAEC of 0.51 mg/m3 is brought forward to the risk characterisation.（中略） In a 90-day oral feeding study of diantimony trioxide groups of 12 male and 12 female Wistar rats of the Alpk:APSD strain were fed diets contaning 0, 1000, 5000 or 20000 ppm diantimony trioxide **(Hext et al., 1999, also reported by CTL, 1997).** Diantimony trioxide, supplied as a white solid with a purity of 99 %, was mixed in the diet and the homogeneity of the mixture was > 95%. No information is provided on the size of the diantimony trioxide particles in the diet, which is likely to affect the gastrointestinal uptake of the substance. The calculated mean daily doses of diantimony trioxide were 84, 421 and 1686 mg/kg bw in males and 97, 494 and 1879 mg/kg bw in females. Cage-side observations were made daily, which included recording changes in clinical condition or behaviour. The body weight of each rat was recorded before exposure started and then once a week until termination. At termination, blood samples were taken and analysed for haematology and clinical chemistry parameters. Complete necropsies were performed on all rats. The adrenal glands, brain, kidneys, liver, epididymides and testes were weighed. All organs and tissues were examined for macroscopic lesions and fixed in 10 % neutral buffered formalin or other appropriate fixative. Tissues from an extensive range of organs from the controls and the top dose group were examined under the light microscope, together with any macroscopically abnormal tissue from the intermediate groups. There was no substance-related effect on food intake, body weight gain or clinical signs of toxicity. A 10 % increase in absolute and relative liver weight was observed in female and male animals in the high dose group along with changes in some clinical chemistry parameters. Male animals in the high dose group showed a 30 % increase in triglycerides (P<0.01) and a 12 % decrease in alkaline phosphatase (P<0.05). Alkaline phosphatase was also decreased in female animals both at 5000 (24 %) and 20000 (37 %) ppm (P<0.01) and in a dose-dependent manner. Cholesterol and aspartate aminotransferase levels were significantly increased in females in the high dose group by 13 and 52 %, respectively. However, no histological changes in the liver were observed to support an adverse effect on liver, and the absence of any other evidence of antimony intoxication suggests that these findings are adaptive to treatment. There was a slight increase in cysts in the pituitary of both sexes in the high dose groups. This was not considered to be treatment related as this is a common spontaneous change in this strain of rats and all values were within the historical control range. Three of the twelve (25 %) males in the high dose group had slight (n=2) or moderate (n=1) plasma cell infiltration in the cervical lymph node. This was not observed in treated females or in any control animal, but according to the evaluation made by the laboratory it has been seen in historical controls but the frequency is not reported. A NOAEL corresponding to 1686 mg/kg bw/d (males) and 1879 mg/kg bw/d (females) can be derived from this study.	別添dossier P 1 （有害性評価書 P3　10行）
(Mutag-enicity) 変異原性	Diantimony trioxide is not considered to induce gene mutations *in vitro*, but induces structural chromosome aberrations in cultured mammalian cells *in vitro*. Oral *in vivo* studies on the induction of chromosome aberrations and micronuclei in the bone marrow and unscheduled DNA synthesis in the liver have produced negative results. It is believed that a possible local genotoxic effect of diantimony trioxide would only be biologically relevant at concentration levels that also cause particle overload. Therefore, there is also no concern for local genotoxicity of diantimony	**4.1.2.7 Mutagenicity** **Conclusion – *In vitro* studies** Negative results were obtained with antimony trioxide in two Ames tests and in a further study using the “spot” technique. Negative results were also obtained in the Mouse Lymphoma TK± assay. Positive results were only obtained in two rec± assays for DNA damage, but it is difficult to draw conclusions on the reliability of this result on the basis of the details provided. One of the Ames assays and the Mouse	

	trioxide in the lung. 三酸化二アンチモンはインビトロで遺伝子変異を誘発しないと考えられているが、インビトロでの哺乳動物細胞の染色体異常を誘発する。骨髄での染色体異常と小核の誘導及び肝臓での不定期DNA合成の誘発に関するインビボ経口試験は陰性だった。三酸化二アンチモンの局所的な遺伝毒性作用は粒子過負荷を生じる濃度レベルで生物学的に関連性があるに過ぎないと考えられている。従って、肺での局所的な遺伝毒性についても懸念はない。	Lymphoma TK± assay were performed according to OECD guidelines. Considering the results obtained in these studies it can be concluded that antimony trioxide does not induce gene mutations *in vitro.* The induction of chromosome aberrations of antimony trioxide was investigated in one study **(Elliot et al,1998)**, which was positive and performed according to OECD guidelines. The induction of SCE of antimony trioxide has been investigated in two studies, which were positive **(Gebel,1997)(Kuroda et al,1991)**. It is concluded that antimony trioxide has the potential to induce structural chromosome aberrations in mammalian cells in vitro. 注）色塗り部分は事務局で補足 **Conclusion – *In vivo* studies** Four *in vivo* mutagenicity studies are available for diantimony trioxide. One micronucleus study on mouse bone marrow, performed in agreement with OECD guidelines and GLP, gave negative results after both single and repeated exposure **(Elliot et al., 1998).** Another study, performed according to OECD guidelines and GLP, where both micronuclei and chromosome aberrations were evaluated in rat, males and females, negative results were obtained after repeated oral dosing with antimony trioxide **(Covance Laboratories Ltd, 2005; Kirkland et al., 2007)**. A rat liver UDS performed according to OECD guidelines did not show any evidence of DNA damaging capacity **(Elliot et al., 1998)**. A mouse bone marrow chromosomal aberration test using a single and a repeated oral dose protocol with antimony trioxide was negative with the single oral dose protocol, but positive with the repeated oral exposure using only male mice **(Gurnani et al., 1992)**. However, due to lethality at the highest dose and unclear reporting of the study, this study is regarded questionable and will not be used for the risk assessment. Consequently, negative results were obtained using OECD test guideline protocols and according to GLP and using two different species – mouse and rat. Therefore, it can be concluded that diantimony trioxide does not cause systemic mutagenicity after oral administration . It should be noted that the absorption of antimony trioxide is only 0.05 % (see section 4.1.2.1), when administered as an oral suspension at a dose of 1000 mg/kg bw, as in the studies above. This means that, despite the high doses that were administrated, the bone marrow may only have been marginally exposed and thus, it is not possible to conclude whether the negative *in vivo* results are due to lack of mutagenic potential or due to inability of the test to detect a mutagenic effect at the low concentrations achieved in the bone marrow following oral exposure. Therefore, it is not possible to conclude whether the results are relevant also for the situation in the lung after inhalation exposure, which is the specific site of contact tissue and the site where tumours have been found in the carcinogenicity studies. However, the *in vivo* data might suggest that a possible mutagenic potency of diantimony trioxide would be low and it is believed that a possible local genotoxic effect of diantimony trioxide would only be biologically relevant at concentration levels that also cause particleoverload. Therefore, there is also no concern for local mutagenicity of diantimony trioxide. **4.1.2.7.3 Summary of mutagenicity** Considering the available genotoxicity data, antimony trioxide does not induce genemutations *in vitro*, but do induce structural chromosome aberrations in cultured mammalian cells *in vitro.* Negative *in vivo* results on chromosome abberations and micronuclei were obtained in two different species – mouse **(Elliot et al., 1998)** and rat **(Covance Laboratories Ltd, 2005)**, **(Kirkland et al., 2007)**. An *in vivo* UDS assay in rats was also negative **(Elliot et al., 1998)**. The tests were performed according to GLP and using	別添dossier P 7 別添dossier P11,15 （有害性評価書 P４　20-24行） 別添dossier P 21 P25 P29 P33 （有害性評価書 P４　25-28行）

		OECD test guideline protocols and oral administration. However, according to toxicokinetik studies, the absorption of a particle suspension of diantimony trioxide after oral exposure is only 0.05 % at the dose of 1000 mg/kg used in these mutagenicity studies, indicating that, despite the high doses that were administrated, the bone marrow may only have been marginally exposed. Therefore, it is not possible to conclude whether the negative *in vivo* results are due to lack of mutagenic potential or due to inability of the test to detect a mutagenic effect at the low concentrations achieved in the bone marrow following oral exposure. Still, it can be concluded that diantimony trioxide does not cause systemic mutagenicity *in vivo* after oral administration. However, it is not possible to conclude on mutagenicity in specific site of contact tissues (local mutagenicity) and thus, whether the result is relevant for the situation in the lung after inhalation exposure, which is the site where tumours have been found in the carcinogenicity studies. However, the *in vivo* data might suggest that a possible mutagenic potency of diantimony trioxide would be low and it is believed that a possible local genotoxic effect of diantimony trioxide would only be biologically relevant at concentration levels that also cause particle overload. Therefore, there is also no concern for local mutagenicity of diantimony trioxide.	
Chronic toxicity/carcinogenicity 慢性毒性／発がん性	Three chronic toxicity/carcinogenicity studies in rats with inhalation exposure to diantimony trioxide were available. The exposure duration in all three animal studies was 12 months only. In the study by Watt, inhalation of 5.0 mg/m3 diantimony trioxide produced lung neoplasms in 44% of the animals tested (only females were exposed). In the study by Groth et al., 45 mg/m3 diantimony trioxide produced pulmonary neoplasms in 32% of the female rats exposed but none in the male rats. The study by Newton et al., showed no lung tumours at any dose level up to 4.5 mg/m3. A comparison of the histopathology tissue sections from the Watt- and the Newton-studies indicated higher lung deposition of antimony and more severe lung damage in exposed rats in the Watt-study than in the Newton-study, which allegedly were conducted at similar exposure levels (1.9-5.0 and 0.06-4.50 mg/m3, respectively). This suggests that the exposure levels in the Watt study were likely higher (5-fold) than those reported, and consequently make the study unsuitable for derivation of a NOAEC. ラットへの三酸化二アンチモンの吸入ばく露による慢性毒性／発がん性の３つの試験が利用できる。３つとも ばく露期間は１２ヶ月。Wattの試験では、5.0 mg/m3の三酸化二アンチモンの吸入で４４％の実験動物（雌のみばく露）に肺腫瘍が生じた。Grothらの試験では、45 mg/m3の三酸化二アンチモンは、雌ラットの３２％に肺腫瘍を生じさせたが、雄ラットでは発生はなかった。Newtonらの試験では、4.5 mg/m3.のレベルまでは肺腫瘍は認められなかった。WattとNewtonの病理組織切片の比較で、 ばく露されたラットは、Wattの試験の方がより高いアンチモンの蓄積とより深刻な肺の損傷があることがわかった。両試験は近いばく露レベルで実施されていたとのことである（それぞれ(1.9-5.0 、0.06-4.50 mg/m3)。このことは、Wattの試験の ばく露レベルは、報告よりも高い（５倍）ことを示唆しており、従ってNOAEC算出には不適切とされる。	**4.1.2.8.3 Summary of carcinogenicity** Three chronic inhalation studies in rats are available for carcinogenicity assessment of diantimony trioxide (Watt, 1983; Groth et al., 1986a; Newton et al., 1994). Two animal studies indicate neoplastic properties of diantimony trioxide, whereas one animal study showed negative results. There is also one human study available (Jones, 1994). However, due to lack of exposure data the human study is regarded inconclusive. The exposure duration in all three animal studies is 12 months and thus all studies deviate from the OECD guideline on chronic toxicity/carcinogenicity, which prescribes an exposure period of 24 months for rats. In the first animal study **(Watt, 1983)** inhalation of 5.0 mg Sb_2O_3/m^3 for 12 months produced lung neoplasms in 44 % of the animals tested (only females were exposed). In the second study, **(Groth et al., 1986a)** a 9 times higher dose (45 mg Sb_2O_3/m^3) produced pulmonary neoplasms in 32 % of the female rats exposed under similar conditions, but none in male rats. It is noted that the female survival rate was significantly higher than the male counterparts in the study by Groth et al., (1986a). The differences in incidence between the studies might be explained by a longer observation period (12 months vs 20 weeks) and by the use of older animals (8 months vs 14 weeks) in the study by Watt (1983). The study by **Newton et al. (1994)** showed no diantimony trioxide-related lung tumours, neither in males nor females, at any dose level up to 4.5 mg/m^3. This is in contrast with the data reported by Watt and Groth and the cause of the difference is not entirely clear. However, the histopathology slides from the negative Newton study was re-evaluated by the pathologist who evaluated the slides from the Groth and of the Watt studies. The re-examination confirmed a lack of diantimony trioxide-related neoplastic changes in the Newton study. In addition, the comparison of the Watt and the Newton studies, which were conducted at similar exposure levels, showed that the exposed rats had more lung damage and appeared to have considerably more antimony deposited in the lungs in the Watt study than in the Newton study. This may suggest that the exposure levels in the Watt study may have been above those reported. Given that the dose level in the study by Groth is 10 times higher and also the dose levels in the study by Watt were likely higher than 1.9 and 5.0 mg/m^3 the dose levels in the Newton study most probably fit in the dose range where no tumous were observed. However, the difference could also be due to different particle generation techniques or different strains of rats. The particle size, which will affect lung deposition,	別添dossier P39 P45 P50 （有害性評価書P5　4,7,11行） （Watt, Newtonは有害性総合評価表参照）

		clearance and retention and hence target organ dose, was similar among the studies although they were all measured using different techniques. (中略)	
	Based on these data it is concluded that diantimony trioxide induces tumours in rat lung. The most likely mechanism for the lung carcinogenicity is impaired lung clearance and particle overload followed by an inflammatory response, fibrosis and tumours. Consequently, diantimony trioxide can be regarded as a threshold carcinogen and the NOAEC of 0.51 mg/m3, derived for local repeated dose toxicity and based on impaired clearance of particles, is also used for carcinogenicity. The NOAEC was determined in a study with a high background incidence of lung inflammation in controls, therefore there is some uncertainty regarding the reliability of the numerical value. これらのデータによると、三酸化二アンチモンは、ラットの肺に腫瘍を誘発すると結論づけられる。肺への発がんの最も起こりやすいメカニズムは、肺のクリアランスの障害と粒子の過負荷、続いて起こる炎症反応、繊維化と腫瘍である。従って、三酸化二アンチモンは、閾値を持つ発がん性物質と見なすことができ、反復投与局所毒性から導出され、粒子のクリアランス障害に基づくNOAEC 0.51 mg/m3が、発がん性にも使用される。このNOAECは、コントロール群の肺の炎症の高いバックグラウンド発生のある試験で決定されたものであるので、数値の信頼性は不確実である。	The issue whether genotoxicity or particle overload may be the reason for diantimony trioxide-induced lung tumors is still not entirely clear. Despite the lack of conclusive data on local genotoxicity in the lung, the overall expert judgement by TC NES is that the most likely mechanism for carcinogenicity appears to be impaired lung clearance and particle overload followed by an inflammatory response, fibrosis and tumours. Consequently, diantimony trioxide can be regarded as a threshold carcinogen and as a starting point for a quantitative risk characterisation the NOAEC of 0.51 mg/m3 derived for local repeated dose toxicity is also used for carcinogenicity. There may be some uncertainty regarding the accuracy of the NOAEC numerical value as the study had a high background incidence of lung inflammation in control animals. In addition, the exposure duration was 12 months and thus deviates from the OECD guideline on chronic toxicity/carcinogenicity, which prescribes an exposure period of 24 months for rats. It could be discussed whether effects caused by pulmonary overload in the rat is also relevant for humans. Positive (Hext, 1994; Oberdorster, 1995) and negative (Tran and Buchanan, 2000; Kuempel et al., 2001) findings of particle overload in human lungs are reported. Macrophage transport of particles into the alveolar interstitium is the major clearance mechanism in humans but of minor importance to the rat. These species differences are related to morphological features of the lung, i.e. to the relative short pathway length from the alveoli to the ciliated terminal bronchioles in rats (Bailey et al., 1989; Kreyling, 1990; Kreyling et al., 1991). In the absence of mechanistic data to the contrary, it must be assumed that the rat model of tumorigenicity can identify potential carcinogenic hazards to humans and the rat presently remains the appropriate model for both neoplastic and non-neoplastic responses to PSP exposure (ILSI Risk Science Institute Workshop Participants., 2000).	
Reproduc-tive toxicity 生殖毒性	No reproductive toxicity studies have been conducted for diantimony trioxide. However, detailed examination of male and female reproductive organs from repeated-dose toxicity studies via the oral route of exposure has been done. Testicular toxicity of diantimony trioxide has been investigated in male mice and male rats. In this 4-week study, diantimony trioxide was administered via gavage to 10 mice and 8 rats/dose at 0, 12.0 and 1 200 mg/kg bw/day, for 5 and 3 days/week, respectively. An oral NOAEL = 1 200 mg/ kg bw/day for testicular toxicity was determined. In a rat 90-day oral feeding study performed according to OECD TG 408 no histopathological changes were observed in testes up to a dose of 1686 mg/kg bw/day, or in ovaries and uterus up to a dose of 1879 mg/kg bw/day. Based on these results, diantimony trioxide was not toxic to male or female reproductive tissues. 三酸化二アンチモンの生殖毒性に関する試験は実施されていない。しかし、経口ばく露の反復投与毒性試験による雌雄の生殖器官の詳細な試験は実施されている。雄のマウスとラットで三酸化二アンチモンの精巣	**4.1.2.9 Toxicity for reproduction** **4.1.2.9.1 Effects on fertility** Testicular toxicity of antimony trioxide was evaluated in rats and mice **(Omura et al., 2002)**.30 male mice (Crj: CD-1) and 24 male rats (Crj: Wistar) were randomly divided into 3 groups at 8 weeks of age, a low exposure group, a high exposure group and a control group, each comprising 10 mice and 8 rats. The antimony trioxide was suspended in distilled water and were administered by gavage; mice, 5 days per week for 4 weeks; rats, 3 days per week for 4 weeks. Four weeks are shorter than the period needed to complete spermatogenesis in rats (approximately 8 weeks) and mice (approximately 39 days). However, the International conference on harmonisation tripartite guidelines on detection of toxicity to reproduction for medical products suggest that a 4-week treatment period is appropriate for detection of drug effects an male fertility in rats, provided that adequate histology and organ weight findings are available from repeat-dose studies. Such examinations were performed in this study, therefore, a 4 weeks administration period was used. The low exposure group was exposed to 12.0 mg antimony trioxide/kg bw/day, the high exposure group was exposed to 1200 mg antimony trioxide/kg bw/day and the control group was administered distilled water. There is no information on the size of the particles, but the purity was > 99.999 %. The mice were kept in an air-conditioned conventional room with a 12h light/12h dark light cycle, 24-26°C and 40-80 % air humidity. Rats were kept in a SPF room with a 12 h light/12 h dark light	別添dossier P59 mice) P65(rats) （有害性評価書 P４　15行）

	毒性が調査された。この４週間試験で、雄マウス１０匹と雄ラット８匹に三酸化二アンチモンが、0, 12.0, 1200 mg/kg bw/dayの用量で 週5日と3日で強制経口投与された。精巣毒性の経口のNOAELは1200 mg/ kg bw/dayとなった。OECD TG 408に基づいて実施されたラットの90日経口投与試験では、精巣で用量1686 mg/kg bw/dayまで、卵巣と子宮で1879 mg/kg bw/dayまで、病理組織的変化は観察されなかった。これらの結果によれば、三酸化二アンチモンは、雌雄の生殖組織に対して毒性はなかった。	cycle, 22-25 °C and 50-60 % air humidity. One day after the final administration, the animals were killed by inhalation of carbondioxide. The testes, epididymidis, ventral prostate and seminal vesicle were removed and weighed. The seminal vesicle was weighed without fluid. In addition, the number, motility and morphology of sperm in the cauda epididymidis and histological changes in the testis were investigated. Sperm motility findings of mice were not included in the report due to “too long interval between removal of the epididymidis and sperm motility analysis”. In the histopathologic examination of the testis, all round or ovoid cross-sections of the seminiferous tubule (173-449 cross sections in rats and 55-165 cross sections in mice) in one transverse section were examined. The following histopathologic changes were examined:disorganisation and exfoliation of the seminiferous epithelium, degeneration of germ cells, vacuolisation of the epithelium, sperm retention in the epithelium and delayed spermiation. Two mice and one rat in the high dose group and one control mouse died due to accidents at administration. No other deaths occurred. No effects on body weight gain of mice or rats were observed. A small, but not statistically significant, decrease in seminal vesicle weight was observed in mice in both the low and high dose exposure groups. This effect was not observed in rats of either exposure group. In both species, the weights of the other organs in the antimony-treated groups were comparable to the controls. No effects on the count, motility or morphology of sperm in the cauda epididymidis in rats or the count, and morphology of sperm in mice were observed in any of the two dose groups.Delayed spermiation was found in one of the 8 rats in the low dose group and one of the 7 rats in the high dose group. However, the frequencies of delayed spermiation in these two rats were less than 1 %. One of the 10 mice in the low dose group showed exfoliation of the seminiferous epithelium; the frequency in this mouse was greater than 50 %. However, this was not observed in mice in the high dose group or rats in either of the groups and therefore this was suggested to be a non-treatment related finding. This study indicates that a repetitive gavage administration of antimony trioxide to rat (3days/week) and mouse (5 days/week) at a dose of 1200 mg/kg bw for 4 weeks was not toxic to testes. The concentration of antimony in testes was not stated. An oral NOAEL of 1200 mg/kg bw for testicular toxicity is suggested. In a 90-day oral feeding study of antimony trioxide (further described in the section Repeated dose toxicity) groups of 12 male and 12 female Wistar rats of the Alpk:APSD strain were fed diets containing 0, 1000, 5000 or 20000 ppm antimony trioxide corresponding to mean daily doses of 84, 421 and 1686 mg/kg in males and 97, 494 and 1879 mg/kg in females **(Hext et al., 1999, also reported by CTL, 1997).** According to the authors the test protocol conforms to modern guidelines. Complete necropsies were performed on all rats. The epididymis and testes were weighed. Epididymis, testes, prostate gland, seminal vesicle, ovary and uterus were examined for macroscopic lesions and fixed in 10 % neutral buffered formalin or other appropriate fixative. These tissues from the controls and the top dose group were examined under the light microscope, together with any macroscopically abnormal tissue from the intermediate groups. No changes were seen in the female or male reproductive organs. An oral NOAEL of 1879 mg/kg, based on no histopathological changes reported for female (ovary and uterus) and male (epididymis, testes, prostate gland, seminal vesicle) reproductive organs, is suggested from this study. **4.1.3.2.7 Toxicity for reproduction** **Effects on fertility**	别添dossier P71

		A gavage study on male mice showed no testicular toxicity after four weeks repeated exposure up to 1200 mg/kg bw. In a rat 90-day oral feeding study no histopathological changes were observed in epididymis or testes up to a dose of 1686 mg/kg/d nor in female reproductive organs up to a dose of 1879 mg/ kg. Therefore, there is no concern for male or female fertility and **conclusion (ii)** is reached .	
Develop-pmental toxicity 発生毒性	The developmental toxicity of diantimony trioxide has been investigated, following a test protocol based on the OECD TG 414. However, some alterations in the conduct of the study have been made. Twenty-six mated rats per group were exposed (nose-only) from day 0 to day 19 of gestation at concentrations of 0, 2.6, 4.4 or 6.3 mg diantimony trioxide/m3. No evidence of developmental toxicity was observed in rats at doses up to 6.3 mg diantimony trioxide/m3 and the NOAEC for developmental toxicity was 6.3 mg/m3, the highest exposure level tested. The LOAEC for maternal toxicity (acute pneumonia and significantly increased absolute and relative lung weights relative to controls) in this study was 2.6 mg/m3. However, body weight and food intake were not affected at any dose level. 三酸化二アンチモンの生殖毒性が、OECDのTG414に基づく試験法に従って行われた。しかし、試験方法は少し変更された。 1 群26匹の交尾後のラットが妊娠期間０～19日の間、0, 2.6, 4.4, 6.3 mgSb2O3/m3の濃度で鼻部ばく露された。ラットで6.3 mgSb2O3/m3の用量まで発生毒性の証拠は観察されず、発生毒性のNOAECは最高のばく露レベルの6.3 mgSb2O3/m3となった。この試験での母体毒性（急性肺炎及びコントロールに比べて絶対的及び相対的な肺重量の有意な増加）のLOAECは2.6 mg/m3であった。しかし、体重及び食物摂取量は、どの用量でも影響はなかった。	**4.1.2.9.2 Developmental toxicity** To determine the developmental toxicity of antimony trioxide, three treatment groups and one control group, each containing 26 female Sprague-Dawley [Crl: CD®(SD)IGS Br] rats, were exposed to diantimony trioxide and clean air respectively, through nose-only inhalation **(MPI, 2003).** A purity of Sb_2O_3 of 99.87% is stated. The study was conducted in accordance with Standard Operating Procedures and was based on the draft guideline published in the US EPA Health Effects Test Guidelines, Inhalation Developmental Toxicity Study, Office of Prevention, Pesticide, and Toxic Substances (OPPTS) 870.3600, issued June 1996 and the OECD Guideline Number 414, Prenatal Developmental Toxicity Study (2001 01 22). However, some alterations in the conduct of the study have been made. The dose intervals are not according to guidelines. Low and mid dose give almost the same internal dose (antimony level in RBC) and the high dose does not give any maternal toxicity. Prior to exposure the female rats were mated to untreated male rats of the same strain and the day on which positive evidence of mating (vaginal plug and/or sperm) was observed was considered Day 0 of gestation. The females were approximately 10 weeks old and weighed between 193 and 270 g on Day 0 of gestation. The mated females were exposed from Day 0 (fertilization) to Day 19 (one day prior to scheduled euthanasia and laparohysterectomy) of gestation, six hours per day, at concentrations of 2.6 (SD ± 2.43), 4.4 (SD ± 3.88), and 6.3 (SD ± 4.18) mg diantimony trioxide/m_3. Control females received clean air by the same procedure and dosing regime as the treated females. This dosing regime was, according to the authors, proposed to identify possible effects on preimplantation loss of the fertilized ova as well as effects on the developing foetus *in utero*. （中略） In conclusion, this study showed no statistically significant developmental toxicity at 2.6, 4.4 or 6.3 mg diantimony trioxide/m_3. A dose related increase in lung weight and a diffuse accumulation of pigmented alveolar macrophages, which likely reflected phagocytosis and accumulation of the test article particulate matter, was observed in the dams. Scattered foci ofacute inflammation (0/10, 7/10, 4/10 and 6/10 in control, 2.6, 4.4, and 6.3 mg/m_3 groups respectively) and type II cell hyperplasia (0/10, 5/10, 4/10 and 5/10 in control, 2.6, 4.4, and 6.3 mg/m_3 groups respectively) were also observed. It should also be noted that the exposure doses in this study were close in the three exposure groups. This is also reflected in the mean level of antimony in RBC, which did not show a dose dependent increase. The concentration of antimony in RBC was almost the same in the two lowest groups and barely twice as high in the highest dose group. This indicates that not three different dosage groups, which is the minimum number of dosage groups recommended in The OECD guideline 414, were achieved in this study. Maternal toxicity (increased lung weight, scattered foci of acute inflamation and type II cell hyperplasia) was observed at 2.6 mg/m_3. However, food intake and maternal body weight were not affected at any dose level. This study suggests that the NOAEC for developmental toxicity is 6.3 mg/m_3, the highest exposure level evaluated. **4.1.3.2.7 Toxicity for reproduction**	別添dossier P77 （有害性評価書P3 35行）

		Developmental toxicity For developmental toxicity there is only one acceptable animal study available. However, it should be noted that the dose intervals are not according to guidelines and the high dose does not give relevant maternal toxicity. This inhalation study, with exposure 6 h/day throughout gestation, showed no statistically significant developmental toxicity at 2.6, 4.4 or 6.3 mg diantimony trioxide/m^3. There is no concern for developmental toxicity and **conclusion (ii)** is reached.	

SIAP：SIDS Initial Assessment Profile　(SIDS初期評価プロファイル)

SIAR：SIDS Initial Assessment Report　(SIDS初期評価レポート)

SIDS：Screening Information Data Set（スクリーニング用情報データセット）

SIDS Dossier:資料集