THE SCIENTIFIC COMMITTEE ON COSMETIC PRODUCTS AND NON-FOOD PRODUCTS INTENDED FOR CONSUMERS

OPINION

CONCERNING

ZINC PYRITHIONE

COLIPA n° P81

Adopted by the SCCNFP during the 22nd plenary meeting
of 17 December 2002

1. Terms of Reference

1.1 Context of the question

Cosmetic products marketed in the EU may only contain those preservatives which are listed in Annex VI of the Cosmetics Directive 76/768/EEC, "List of preservatives which cosmetic products may contain".

The preamble of the Annex states that preservatives marked with the symbol (+) may also be added to cosmetic products in concentrations other than those laid down in the Annex for other specific purposes apparent from the presentation of the products.

Zinc pyrithione bears the symbol (+) and can therefore be used in cosmetics at higher concentrations, as long as they are not employed as preservatives.

In its opinion of 17 February 1999 concerning the restrictions on materials listed in Annex VI of Directive 76/768/EEC on cosmetic products, the SCCNFP stated that those substances indicated by (+) in Annex VI, when incorporated into cosmetic formulations for non-preservative functions, should be subjected to the same restrictions in usage levels and warnings as when used for preservative effects.

If a preservative marked with the symbol (+) is added for non-preservative purpose to a cosmetic product in a concentration higher than that laid down in the Annex VI, data to substantiate its safety should be submitted to the SCCNFP.

1.2 Request to the SCCNFP

The SCCNFP was requested to review the data submitted to support the safety of zinc pyrithione, when used at concentrations other than those laid down in Annex VI to Directive 76/768/EEC :

* Can zinc pyrithione safely used for non-preservative purposes in cosmetic rinse-off and leave-on hair care products at a maximum concentration of respectively 1.0 and 0.1 %?

* Can zinc pyrithione safely used for preservative purposes in cosmetic rinse-off hair care products at a maximum concentration of 1.0 %?

* Does the SCCNFP propose any restrictions or conditions for its use in cosmetic products?

1.3 Statement on the toxicological evaluation

The SCCNFP is the scientific advisory body to the European Commission in matters of consumer protection with respect to cosmetics and non-food products intended for consumers.

The Commission's general policy regarding research on animals supports the development of alternative methods to replace or to reduce animal testing when possible. In this context, the SCCNFP has a specific working group on alternatives to animal testing which, in co-operation

with other Commission services such as ECVAM (European Centre for Validation of Alternative Methods), evaluates these methods.
The extent to which these validated methods are applicable to cosmetic products and its ingredients is a matter of the SCCNFP.

SCCNFP opinions include evaluations of experiments using laboratory animals; such tests are conducted in accordance with all legal provisions and preferably under chemical law regulations. Only in cases where no alternative method is available will such tests be evaluated and the resulting data accepted, in order to meet the fundamental requirements of the protection of consumer health.

2. Toxicological Evaluation and Characterisation

2.1. General

2.1.1. Primary name

Zinc pyrithione (INCI name)

2.1.2. Synonyms

bis [1-hydroxy-2(1 H)-pyridine-thionato] zinc (IUPAC)
Pyrithione zinc
ZP, ZnPT, ZnPTO
Zinc bis(2-pyridylthio)-N-oxide
Zinc pyridinethione
Zinc 2-pyridinethione-l-oxide
Bis (N-oxopyridine-2-thionato) zinc (II)
BOTZ

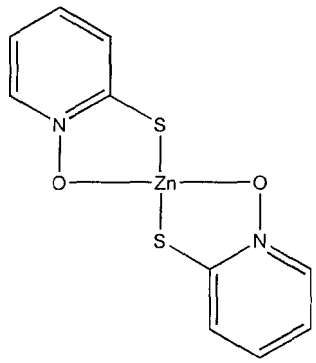
2.1.3. Trade names and abbreviations

Zinc Omadine
Vancide ZP

2.1.4. CAS no.

CAS n° : 13463-41-7
EINECS n° : 236-671-3

2.1.5. Structural formula



2.1.6. Empirical formula

Emp. Formula : $C_{10}H_8N_2O_2S_2Zn$
Mol. weight : 317.7

2.1.7. Purity, composition and substance codes

/

2.1.8. Physical properties

Appearance : white to slightly yellow crystals
Melting point : 240 °C
Boiling point : /
Density : 1.782 at 25 °C
Rel. vap. dens. : /
Vapour Press. : /
Log P_{ow} : /

2.1.9. Solubility

Very low solubility in most solvents.

Water	:	0.0015	w/w %
Ethanol	:	0.031	w/w %
Acetone	:	0.07	w/w %
Chloroform	:	0.34	w/w %
Mineral oil, light	:	0.0001	w/w %

2.2. Function and uses

Authorised as a preservative in rinse-off products at a maximum concentration of 0.5%. Its use is forbidden in products for oral hygiene.

Presently, the only reported "other use" is as an anti-dandruff agent in hair care formulations.

Requested use : - cosmetic rinse-off hair care products at a maximum concentration of 1.0 %
- cosmetic leave-on hair care products at a maximum concentration of 0.1 %
- as a preservative in cosmetic rinse-off hair care products at a maximum concentration of 1.0 %.

TOXICOLOGICAL CHARACTERISATION

2.3. Toxicity

2.3.1. Acute oral toxicity

Ingredient based data

LD_{50} values for zinc pyrithione have been determined in various species after oral administration. The values in the rat ranged from 92 to 266 mg/kg and in the mouse from 160 to 1000 mg/kg. Six hundred mg/kg was found to be the LD_{50} when administered orally to dogs.

Ref. : 6, 10, 33, 57, 71, 73

Product based data

The oral LD_{50} values for shampoo formulations containing zinc pyrithione have been established in rats as 2.5 g/kg for a cream shampoo and 3.0 ml/kg for a lotion shampoo. An analysis of the acute data for rats from a number of studies provides the following mortality/dose levels :

Lethal dose	*Cream shampoo (g/kg)*	*Lotion shampoo (ml/kg/*)*
LD_1	1.4	4.5
LD_{25}	2.0	2.4
LD_{50}	2.5	3.0
LD_{75}	3.1	3.9
LD_{100}	4.5	6.0

* The density of the lotion shampoo form is approximately 1, and for practical purposes, g and ml may be interchanged

In addition, Snyder et al (1965) studied the acute oral toxicity of the cream shampoo product with higher levels of ZPT and estimated the LD_{50}. The results showed that increasing the level of ZPT increases acute oral toxicity.

Ref. : 61

Emetic studies in dogs and pigeons showed that zinc pyrithione in this formulation is a potent emetic. A summary of the results follows :

Emetic dose	***Cream shampoo (g/kg)***	***Lotion shampoo (ml/kg/*)***
LD_0	0.007	0.04
LD_{50}	0.02	0.07
LD_{100}	0.07	0.25

For the cream shampoo form in pigeons, the ED_{100} was 0.1 g/kg, the ED_0 was 0.02 g/kg, and the ED_{50} was approximately 0.05 g/kg.
The effect of the level of zinc pyrithione in the cream shampoo formulation upon the emetic potential in dogs is shown in the following table :

ZPT (%)	*Emetic Dose (g/kg)*		
	ED_0	*ED_{50}*	*ED_{100}*
0	0.2	0.6	1.6
2	0.007	0.02	0.07
3	0.006	0.015	0.025
5	0.006	0.006	0.025

In the emetic studies with dogs, the emesis typically occurred within 60 minutes of dosing, the average being 30 minutes, and involved two to four episodes. Occasional bloody vomitus was seen, indicating gastric irritation.

Overall, the ratios of ED_{50} to LD_{50} for both forms of the product are 1:125 for the cream shampoo and 1:42 for the lotion shampoo; therefore, it is unlikely that a human accidentally ingesting shampoo could retain a hazardous amount. This assumption is supported by the safe marketing history of zinc pyrithione containing cosmetic shampoos. For example, during this time a number of cases of accidental ingestion of shampoo have been reported. In none of these cases were there any serious side effects.

Ref. : 14, 15, 38

2.3.2. Acute dermal toxicity

Ingredient based data

Dermal LD_{50} values for albino rabbits that range from < 2,000 mg/kg to 10,000 mg/kg.

If the dose levels required to obtain dermal LD_{50} values are compared to values for other routes of administration, it is evident that ZPT toxicity is much reduced by cutaneous application, and therefore only a minimal risk exists from this type of exposure. This conclusion has been verified in several studies which are reported under point 2.7. Toxicokinetics and it is supported by comparison of those data with no-effect levels determined in lifetime feeding studies in animals.

Ref. : 66*

Product based data

A shampoo containing 2% ZPT at levels of 2.5, 5.0, 10.0, and 20.0 g/kg was tested on rabbits. The shampoo was occluded with a rubber sleeve and left in place for 24 hours. There were no observable systemic effects in animals treated with 2.5, 5.0, or 10.0 g/kg. Two of the four animals dosed with 20 g/kg showed a slight temporary depression. There were no deaths at any level. These data are in line with a study on ZPT alone indicating that its incorporation into a shampoo formulation does not significantly enhance penetration.

Ref. : 61, 67

In addition, intraperitoneal and intravenous data were provided for comparison to the oral and dermal data.

Intraperitoneal

Intraperitoneal injection of ZPT resulted in LD_{50} values of 36 mg/kg for rats and 500 mg/kg for mice.

Ref. : 71, 73

Intravenous

Generally, 25 mg/kg of ZPT was fatal to both dogs and monkeys within 24 hours and produced cholinergic-like effects prior to death. Doses of 15 and 20 mg/kg produced slight cholinergic stimulation in dogs but death did not result. One of two Yorkshire pigs died when injected intra-venously with 20mg/kg and 10 mg/kg was a lethal dose for rabbits. Intravenous doses of 5 mg/kg or less produced only transient effects.

Ref. : 2, 7, 72

2.3.3. Acute inhalation toxicity

No data

2.3.4. Repeated dose oral toxicity

No data

2.3.5. Repeated dose dermal toxicity

No data

2.3.6. Repeated dose inhalation toxicity

No data

2.3.7. Sub-chronic toxicity

Ingredient based data

No significant effects have been noted other than the hind-limb weakness or paralysis which occurred in rats and rabbits within 8 to 14 days when ZPT was administered in the diet at levels from 165 ppm to 330 ppm (8-16 mg/kg/day). Doses greater than 330 ppm required longer periods of administration before paralysis occurred. At levels of 1000 ppm or greater the animals usually died without developing a paralysis. The dose/time response with respect to paralysis is not yet completely understood, since it is complicated by several variables that are discussed below. With respect to paralysis, a NOEL of 0.5 mg/kg/day (500 µg/kg/d) has been determined in two year feeding studies in rats. At this dose no toxic effects were observed over the two year study period.

Hind-limb Paralysis

Several studies have been conducted to determine the dose range that produces paralysis, the reversibility of this effect, and the ultrastructural cellular changes involved. The results of these studies have been fully considered as part of the safety evaluation of ZPT.

In many of the studies reported, ZPT was added to the diet of the animals, and its level is therefore expressed as parts per million (ppm). Also, some of the studies began with young rats (approximately 100 g of body weight) and were concluded after the animals were full-grown (approximately 400 g). The amount of ZPT the animals ingested generally increased with age but not in direct proportion to their weight. Also, in some of the studies, addition of ZPT to the diet caused the animals to eat considerably less than they did prior to addition of the material. Milligram/kilogram equivalents of ppm in the diet have been provided for the studies that follow; however, it must be remembered that they are only approximations for the reasons set forth above.

Hind-limb paralysis was initially noted in a study of sub-chronic toxicity of ZPT by Larson (1956 Groups of young (60-70 g) rats (equally divided by sex, 20/group) had 0, 15, 75, 375, 938 or 1,875 ppm ZPT added to their dry diet for three months. These levels are approximately equivalent to 0, 2.3, 12, 58, 144 and 288 mg/kg/day. Those receiving 1,875 ppm grew poorly and during the second week had diarrhoea and a marked weakness of the hind-limbs. Eight of the each sex died during this period. By the end of the second week, rats receiving 375 ppm had developed similar signs of toxicity, whereas those receiving 938 ppm showed relatively mild effects. The experiment was then terminated on the premise that the diets had been mixed up, and a second study was started. Young rats (20/group, 10 male and 10 female) were given 0, 15, 75, 188, 375 or 750 ppm of ZPT in their diet for three months. Equivalent doses in mg/kg/day are about 0, 2.3, 12, 29, 58 and 115 for young rats and 0, 1.2, 6, 15, 30 and 60 for older animals. In this study, growth and survival were adversely affected at 75 ppm (12 mg/kg/d) and higher dietary concentrations. The animals receiving the 188 ppm dose level showed earlier,

more extensive hind-limb weakness than those receiving the higher doses. Histopathologic examination of tissues from animals in both studies were unremarkable, and no morphological alteration which could be related to the hind-limb weakness was found.

In order to understand better the effects of intermediate dietary levels of ZPT, Ziller (1969) fed rats with diet containing 83, 166, 332, 500 and 664 ppm of ZPT (3.3, 6.6, 13.2, 20 and 26.6 mg/kg/day). He showed that the most rapid onset of hind-limb paralysis occurred at concentrations between 166 and 332 ppm. At these levels the rats had a significant decrease in body weight as the paralysis was developing. Part of this weight loss was due to a significant decrease in food consumption, since the animals had difficulty reaching their food. Data are reported in the table below.

Table : Dietary Levels of ZPT as Related to Onset of Paralysis (Ziller, 1969)

Concentration of ZPT in the diet (ppm)	*mg/kg/day ratio*	*Number of animals affected*	*Time of onset (days)*
83	3.3	2 of 5	34 to 36
166	6.6	5 of 5	10 to 12
332	13.2	5 of 5	10 to 14
500	20.0	5 of 5	15 to 29
664	26.6	1 of 5	29

Since 166 and 332 ppm ZPT in the diet were found to result in paralysis in about the same period of time, an additional study was designed to check the effect at a level near the midpoint of these concentrations.
In this study Ziller (1969) used a young (60 g) group and an older (230 g) group of rats which received 250 ppm (40 and 20 mg/kg/day for the young and older animals, respectively) ZPT in their diets. Both groups developed hind-leg paralysis after ten to twelve days, and tended to eat less prior to when the development of paralysis began. Administration of the control diet led to a reversal of effect (i.e., after four days on control diet, the animals were not considered paralysed). Return to the 250 ppm ZPT diet resulted in paralysis again after about the four more days; feeding again with the control diet clinically normalised the animals in an additional four days. Similar clinical recoveries have been noted by Snyder et al. (1965), Dearwester and Johnson (1974), Opdyke and Burnett (1967), Sahenk and Mendell (1979), and Nelson et al. (1965). Dearwester and Johnson (1974) confirmed the critical dietary levels of ZPT for developing hind-limb paralysis in rats. The results are in line with Ziller's (1969) and Larson's (1956) findings, in that paralysis could be produced within ten days at a level of 250 ppm (approximately 20mg/kg/d). Functionally, the affected animals exhibited hind-quarter paresis in that they were able to use their rear limbs, but only by using them in unison (hopping action) were they able to attain effective movement. The condition was progressive in nature, terminating in death, so long as the animals continued to receive the ZPT-containing diet. Necropsy of affected test animals revealed a marked bilateral hind-quarter muscular atrophy.
Since the rat previously had shown a remarkable ability to recover from paralysis by switching to the control diet, Ziller (1969) undertook the following study. Groups of ten rats were given daily, single doses of either 12.6 mg/kg/d of NaPT or 13.6 mg/kg of ZPT, either by stomach tube (NaPT or ZPT) or by intraperitoneal injection (NaPT) for a four week period. No paralysis or weight loss was observed. This unlikely finding has also been reported by other investigators.

Snyder et al (1965), for example, observed that animals given ZPT in formulation by stomach tube at levels that produce paralysis in feeding studies, suffered no ill effects.
Opdyke and Burnett (1967) also reported that hind-limb paralysis could be produced in rabbits in fourteen days when they were to lick a 10 mg/kg/day application of ZPT off their backs, or off their cages, but that intravenous injection of the same dose produced no symptoms in three weeks.
In the last three studies cited above, which deal with hind-limb paralysis in rats and rabbits, it was reported that the effect is produced only when ZPT is ingested and could not be produced when the material was given through a stomach tube. These apparent discrepancies are explained below.
Gibson (1979) has described a study in which four groups of rats were dosed with ZPT by stomach tube at levels of either 10 or 20 mg/kg/day for either five or seven days a week. When animals were dosed daily with ZPT by stomach tube at levels of either 10 or 20 mg/kg/day, hind-limb paresis progressed rapidly in almost every animal. The major difference between dose levels was the time of onset (6-8 days for 20 mg/kg and 8-10 for 10 mg/kg). When the animals were dosed Monday through Friday and not on weekends, the hind-limb mobility impairment was so slight at the end of the three week experiment that it amounted to no more than an almost imperceptible change in gait. This change may well have been overlooked by previous investigators. The difference in severity of effects produced by dosing either five or seven days a week is probably due to the reversible nature of the paralysis and recovery over the weekend by those animals dosed five days a week.

In order to study the effects of ZPT in the diet of another species, Calvin and Lawhorn (1972a) used rhesus monkeys. Groups of three animals were fed either 0 (control group), 100, 300 or 533 ppm of ZPT mixed with chow for a period of 30 days. These levels correspond to 0, 1.2-1.8, 3.6-5.4 and 6.0-9.0 mg/kg/day respectively. The range reflects the different weights of the animals. At no time did the animals exhibit a test-related change in motor, sensory, or behavioural activity. Histologic examinations of all major organs, central nervous system, and peripheral nervous system showed no abnormal conditions or test-related responses. Also, no test related effects were seen in haematological or blood serum analysis.

Reno and Banas (1975) also studied the effects of ZPT incorporated into the diet of rhesus monkeys at higher levels. In this study the animals were fed diet containing 500 and 5000 ppm of ZPT (12 and 30 mg/kg/day) for 28 days. There were three animals in each test group and two animals in the control group. No adverse effects were observed in the monkeys fed ZPT at the lower dose level. The animals receiving the higher dose level, however, exhibited lethargy, anorexia, weight loss, soft faeces, or diarrhoea, and one of them died on Day 23 of the study. The two remaining animals experienced a 25-30% weight loss over the study, and signs of neurological deficit were noted. The only compound-related histopathology was limited to atrophy of the musculature of monkeys in the high-dose group. There were no unusual findings associated with the peripheral or central nervous system.

As stated previously, the dose/time response for onset of paralysis is not completely understood; however, some complicating variables were known. During the course of many of the studies (rats, rabbits, monkeys) summarised above, the animals failed to gain weight, and some even lost weight. This was due to reduced food consumption, either because of progressing paralysis or because of reduced palatability of chow with higher levels of ZPT added. For these reasons dose/response in terms of mg/kg/day cannot be accurately calculated. Also it seems likely that a critical systemic level of ZPT or a metabolite must be attained and maintained for a

sufficient period of time to produce paralysis. Gibson (1979) has shown that animals partially recover over the weekend when they are dosed 5 days/wk. Intermittent reduced food consumption or food avoidance on some days could produce a similar effect that in turn affects the systemic level.

Follow up studies on hind-limb paralysis (mechanism of action)

The studies that follow were undertaken by investigators to identify the lesion associated with paralysis and to obtain additional information on the mechanism of action.

Work by Snyder et al (1977, 1979), Dejesus et al (1978), Chrisman and Ross (1978) and Sahenk and Mendell (1979, 1979a, 1980) has provided considerable information concerning ZPT-induced paralysis.

Snyder et al (1977) determined that the hind-limb muscle wasting reported by Dearwester and Johnson (1974) was a disuse atrophy secondary to neurologic effects. Using in situ sciatic nerves Snyder et al (1977) found conduction velocities were normal, but they observed a decrease in the force of muscle contraction. Effects on serum cholinesterase were rejected as a possible cause, since levels were measured and found to be normal. Dejesus et al (1978) in a later study confirmed their finding of normal conduction velocities using the sural nerve, but in addition he found a reduction in the amplitude of the sensory potential and a reduction in duration of the evoked response.

Similar studies by Chrisman and Ross (1978) investigated the clinical and electrophysiologic response to several dose levels of ZPT using rats. The animals were fed diets containing 0, 10, 50, 250, 500, 750 and 1000 ppm ZPT for 12 weeks. At a concentration of 10 ppm in the diet (0.6 mg/kg/day), there were no changes in neurologic signs or electrophysiologic function during the course of the study. However, at 50 ppm in the diet (4.0 mg/kg/day for females and 2.6 mg/kg/d for males) severe neurologic deficit and electrophysiologic abnormalities were noted. Reduction in the electrophysiologic response began after about one week on the diet, and neurologic deficit was grossly apparent about a week later. These changes became progressively more pronounced and were most severe at six weeks. After eight weeks on the diet, the animals began to improve, and some of the rats completely recovered clinically. Animals receiving 250 ppm of ZPT in the diet died prior to termination of the study. All of the rats were severely affected, and no recovery was observed prior to death. Concentration of 500 ppm and greater in the diet produced mild or no neurologic deficit or electrophysiologic changes prior to death.

Milligram/kilogram equivalents have not been provided for dietary concentration of ZPT above 50 ppm because of excessive body weight loss and extreme variability in the amount of chow eaten.

The work by Chrisman and Ross (1978) is especially important in that it confirmed the no-effect level [10 ppm (0.6mg/kg/d) of ZPT in diet] determined by Larson (1958) in the chronic feeding study summarised below. In addition to confirming the NOEL, the work also serves to point out the sensitivity of the rat to the neurologic effects of ZPT (see also Sahenk and Mendell (1980)).

Since ZPT is applied topically in shampooing, its toxicity after cutaneous application has been studied. Several sub-chronic toxicity studies have been conducted in which ZPT was applied to the backs of rabbits and mice. Ingestion of applied material occurred in some of these studies and is noted below.

Larson (1957) conducted a 90-day percutaneous toxicity study with ZPT (2 ml of water per gram of 50% wettable ZPT powder) using albino rabbits. Doses of 125, 250, 500, 1000 and 2000 mg/kg were applied daily (5 days per week) to groups of three or four animals for 13 weeks. The animals were harnessed during application and remained so until the material dried, at which time the animals were washed. None of the rabbits receiving 1000 or 2000 mg/kg survived the 90-day test period, the longest survival being 21 days. Four of twelve animals dosed at the lower levels survived, and those were necropsied at that time. Focal necrosis of either the brain or spinal cord in three of the four surviving animals. There were no histological changes in other organs.

Nelson et al (1965) also conducted studies on the toxicity of ZPT applied topically to rabbits. The material was left in contact with the skin during the periods between application and no effort was made to preclude ingestion of the ZPT. Dosage was daily, and ranged from 50 to 480 mg/kg. After 7 to 15 daily treatments, the rabbits developed hind-limb weakness and diarrhoea. With continued treatment, weakness of both forelegs and death occurred. Treatment was discontinued in three instances coinciding with the onset of severe quadraparesis in two animals and mild quadraparesis in the third rabbit. All three animals recovered. Histopathological observation after autopsy of severely paralysed rabbits revealed no significant structural alterations in the brains, spinal cords, peripheral nerves, muscles, and abdominal or thoracic viscera in 8 of 12 rabbits. In the other four rabbits various alterations in CNS tissue were seen that the author associated with a protozoan infection.
In work conducted at Food and Drug Research Laboratories, cited by Snyder et al (1965), two groups of six rabbits received daily topical applications, five days a week, of 5 ml of a 20% aqueous paste of a commercial soap, with or without 1 % ZPT (on a soap basis). This amounts to 10 mg/kg/day. The animals were kept in stocks for six hours after treatment, at which time the skin was washed and dried, and the animals were returned to their cages. There was a total of 65 applications, equivalent to 50 mg/kg/week. No difference was noted in skin effects or in gross or microscopic pathology between the test group and the control group treated with soap alone. No effects on the eye were seen in either group. Histopathologic study of the brains of both groups revealed changes frequently seen in laboratory rabbits that are thought to be associated with the protozoan organism Encephalitozoon cuniculi. This condition is spontaneous, is seen with great frequency, and is mild chronic in nature. There were no compound-related lesions.

In addition to the rabbit studies, two sub-chronic mouse percutaneous toxicity studies were conducted and are summarised below. A six-week study by Dobbs and Nixon (1973) was conducted to determine dose levels of ZPT for an eighteen-month dermal carcinogenicity bioassay study that would not cause systemic toxicity from oral ingestion during grooming. Ten female mice were used per test material and dose level; five were group-housed, and five were housed individually. Application of 0.1 ml of undiluted test material was made five times per week to a 2 x 2 cm clipped area of the interscapular skin for six weeks. Test materials were ZPT at 0.08, 0.4 and 2.0% in a 1 % surfactant (triethanolamine lauryl sulfate)/ 0.5% thickener (Methocel) aqueous slurry, and a vehicle control. These levels correspond to approximately 0.28, 1.4, and 7.0 mg/kg/day. Four animals, two group-housed and two single-housed, treated with the mixture containing 2% ZPT were necropsied after six weeks of treatment, and no gross

abnormalities were observed. None of the treatments produced local or systemic effects after a total of 30 applications (six weeks). The study was terminated at this point.
Another mouse study to determine maximum tolerable cutaneous doses of ZPT in a 1 surfactant/0.5% thickener vehicle was conducted by Gargus (1974). Groups of 30 mice (15 male and 15 female), individually housed, were treated topically three time weekly for four weeks with 0.1 ml doses of 0.4, 2.0 and 10.0% (10, 50 and 250 mg/kg/application) ZPT. The high dose group had the 10% concentration applied for one week, and since no toxicity was observed, a 20% concentration (500 mg/kg/application) was substituted for an additional three weeks. After four weeks no skin irritations or other toxicity was observed for animals treated with 0.4 and 2.0% concentration of ZPT. Animals treated with 20% ZPT showed thickening of the skin and erythema. No hind-limb paralysis as observed in rats or rabbits was seen in any of the groups.

From the Snyder et al (1965) study, one can conclude that a dose level of 10 mg/kg/day of ZPT applied topically to rabbits is a no-effect level. Interpretation of the rabbit studies by Larson (1957) and Nelson et al (1965) summarised above, is complicated by several factors. Depending on what Larson (1957) used to wash the animals, some material probably remained on the skin and was subsequently ingested. Nelson et al (1965) study, and the uncertainty regarding ingestion in these studies make any conclusions tentative, at best. That ingestion of ZPT occurred in these studies can be supported by examining dose levels used in teratology studies conducted by Nolen et al (1975, 1979). He reported that application of 25 to 100 mg/kg/day of ZPT to the backs of rabbits produced no adverse effects when ingestion was meticulously prevented. Therefore, 100 mg/kg/day instead of 10 mg/kg/day is a better estimate of a no-effect level for topical administration to rabbits. The no-effect level in mice for percutaneous toxicity is approximately 100 mg/kg/day, and the effect level (local irritation) is approximately 200 mg/kg/day.

Product based data

In sub-chronic oral toxicity studies conducted by Snyder et al (1965) four rats (two males and two females) received a daily dose by stomach tube of shampoo containing 10% ZPT, at a level of 10 mg/kg/day of ZPT 5 days/week for three weeks. The rats tolerated the dose without apparent effect.
Additional studies were performed by Snyder et al (1965) on groups of 13 weaning (50 g) rats. The ZPT was incorporated in the diet in the form of the shampoo and was fed on an interrupted schedule over a nine-week period, as described below. A control group received a ground basal diet; a second group received a diet containing 50 ppm of ZPT, and a third group received a diet containing 250 ppm of ZPT. The doses for the weaning animals were approximately 10 and 50 mg/kg/day for the two levels. Doses for adults animals were approximately 4 and 20 mg/kg/day. Rats fed the diet containing 250 ppm of ZPT from shampoo showed typical skeletal muscle paralysis after one week, at which time they were put on the control diet. Six weeks after being returned to the basal diet, the body weights of this group were within 15 g of the control group. At that time they were put back on the diet containing 250 ppm ZPT from shampoo. In about two weeks, signs of paralysis were once again observed. The animals were again put on the basal diet and again recovered from the paralysis. The group fed the diet containing 50 ppm of ZPT gained about 100 g less during the nine-week period than the controls. These animals were not completely paralyzed, but a muscle weakness was observed. At the end of the experiment, the animals were placed on a basal diet, and the observed paralysis disappeared.

Snyder et al (1965) also reported studies in which four groups of two rabbits each received a shampoo formulation containing 10% ZPT incorporated in the diet at levels supplying 0, 3.5, 17.5, and 70.0 mg/kg/day of ZPT for 21 days. The animals showed no effects when fed the diet containing shampoo (10% ZPT) at a level supplying 35 mg of shampoo (3.5 mg ZPT) per kilogram per day for two weeks. At levels of 175 and 700 mg of shampoo (17.5 and 70.0 mg ZPT/kg/day), the animals developed gross signs of toxicity within two weeks. They became listless and disinclined to move, unable to sit in a normal position, and were frequently observed half sitting and half lying. After several days they could no longer get up to eat or drink. Death (except for animals sacrificed) was assumed to be due to starvation.

In another study, four groups of six rabbits each received the same product described above at doses supplying ZPT at levels of 0, 20, 40, and 80 mg/kg/day five days per week for three weeks. The material was administered in single daily doses with a stomach tube. No signs of toxicity were observed. This study supports the concept discussed in the ZPT safety summary below, that dosing of ZPT requires exposure to the test compound seven days per week.

Snyder et al (1965) also studied in dogs, the subchronic effects of oral administration of a shampoo containing 2% ZPT. The material was administered by stomach tube or in capsules. Emesis was regularly produced in mongrel dogs given shampoo containing 2% ZPT at doses of 50 mg/kg (1 mg ZPT/kg) and above. Doses as high as 5 g/kg (100 mg ZPT/kg), well above the LD_{so} level for rodents, produced emesis, but no other effects were seen over a two-week observation period. To determine possible cumulative effects under these conditions, a single mongrel dog was given oral doses of shampoo at the level of 1 g/kg three times a week for eight weeks and of 5 g/kg three times during the ninth week. Emesis occurred after each dose, at intervals between 30 minutes and 200 minutes. Despite some relatively long retention times, body weight was maintained, and the animal appeared healthy. There were no apparent neurologic or ocular effects.
Using yet another species, Snyder et al (1965) administered a 10 mg/kg dose of ZPT, as a shampoo containing 10% ZPT, by stomach tube to a monkey five times weekly for 16 weeks. The monkey showed no apparent signs of muscle weakness, paralysis, or damage to the retina. These results are in line with those of Reno and Banas (1975) who reported that 12 mg/kg day of ZPT produced no adverse effects in monkeys during a 4-week test period.

Orally administered ZPT in a shampoo formulation produces a reversible paralysis in rats and rabbits within one to two weeks at levels of 10 mg/kg/day. A dose level of 10 mg/kg/day of ZPT in shampoo was used in a monkey gavage study which lasted 16 weeks. No adverse effects were observed. Because of the emetic potential of shampoos, oral dosing of dogs has not produced any toxic symptoms, including ocular effects. The value of an emetic product has been discussed in the section on acute toxicity.

Table : Summary of Sub-chronic Oral Toxicity Data for Products Containing ZPT

Species	*Number of Animals*	*Route of administration*	*Dose [a] ZPT*	*Dosage (days)*	*Observation*
Rat	4	Stomach tube	10 mg/kg/day	15	No effects
Rat	13	Diet	1 mg/20 g diet [b]	63	Muscle relaxation
Rat	13	Diet	5 mg/20 g diet [c]	7	Muscle relaxation
Rabbit	2	Diet	3.5 mg/kg/day	14	No effects

Rabbit	2	Diet	17.5 mg/kg/day	14	Muscle relaxation
Rabbit	2	Diet	70 mg/kg/day	14	Muscle relaxation
Rabbit	6	Stomach tube	20 mg/kg/day	15	No symptoms
Rabbit	6	Stomach tube	40 mg/kg/day	15	No symptoms
Rabbit	6	Stomach tube	80 mg/kg/day	15	No symptoms
Rabbit	4	By mouth [d]	15 mg/kg/day	20	No paralytic symptoms
Dog	2	Oral	25 mg/kg/day [e]	14	Emesis, pupil dilation, blindness
Dog	4	Stomach tube	1 mg/kg/day	1	Emesis
Dog	1	Stomach tube	20 mg/kg	3 d/week for 8 w	Emesis
			100 mg/kg	3 d/week in week 9	emesis
Monkey	1	Stomach tube	10 mg/kg/day	80	No effects
Monkey	2	Stomach tube	25 mg/kg/day	8	Emesis and diarrhoea
Monkey	3	Diet [f]	1.2-1.8 mg/kg/day	30	No effects
Monkey	3	Diet [f]	3.6-5.4 mg/kg/day	30	No effects
Monkey	3	Diet [f]	6.0-9.0 mg/kg/day	30	No effects

[a] Dosed as shampoo base containing 10% ZPT, except where indicated
[b] 20mg/kg/day for 50 g weanlings; 5 mg/kg/day for 9-week weight of approx. 200 g
[c] 100 mg/kg/day for 50 g weanlings; 20 mg/kg/day for 7-week weight of approx. 250 g
[d] Ten divided daily doses
[e] Dosed as w/o emulsion
[f] ZPT palletised with food

In initial sub-chronic percutaneous toxicity studies with a 2 % ZPT shampoo, toxic effects were noted. Observation of later studies showed that the animals were ingesting test products by licking. When the animals were restrained from licking in these tests, toxic effects were no longer seen.
Snyder et al (1965) reported on two studies in which the percutaneous toxicity of the shampoo formulation with an exaggerated level of 10% ZPT was tested on restrained rabbits. In one study, two groups consisting of ten albino rabbits each received daily doses (five days a week for 13 weeks) at levels of 2 ml/kg of a 7.5% solution (15 mg/kg of ZPT) of the shampoo. The material was applied to shaved intact skin. An additional group of nine rabbits also received daily doses (five days a week for four weeks) at levels of 2 ml/kg of a 10% solution of the shampoo containing 10% ZPT (20 mg/kg of ZPT), which was applied to abraded skin. In the study on non abraded skin where rabbits were dosed five times per week with 15 mg/kg/day for 13 weeks, no gross signs attributable to penetration were observed, nor was there any histological evidence of toxicity at the end of the test period following a standard necropsy. Furthermore, application of 20 mg/kg/day (100 mg/kg/week) for four weeks to the abraded skin of rabbits resulted only in irritation. There was no evidence of toxicity in either group based on gross appearance, average body weights, haematology values, and microscopic tissue examination.

Summary

* ZPT produces a reversible paralysis when fed to rats and rabbits at levels from 75 to 750 ppm (approximately 12 - 115 mg/kg/d) as part of the diet
* a concentration of 250 ppm (approximately 38 mg/kg/d) in diet seems to be the concentration at which the effects are most rapidly produced
* monkeys do not become paralysed when fed ZPT at levels of from 100 to 500 ppm (1.2 to 12.0 mg/kg/day) for up to 30 days, but signs of neurologic deficit have been observed at a dose level of 5000 ppm (30 mg/kg/day)
* neurological effects seen in some animal species exposed orally to ZPT may not be demonstrated by the dermal route of exposure where ingestion was controlled
* dermal application of 10% solutions of shampoo formulations containing up to 20 mg ZPT/kg/d produced only mild to moderate irritation in rabbits.

These studies were designed to produce toxic effects so that dose response and reversibility of paralytic effects could be studied. The studies serve to point out the sensitivity of the rat to ZPT-induced toxicity. While the monkey may be a highly-appropriate model for predicting human safety, using the more vulnerable rat model builds additional conservatism into the calculation of safety factors. Additionally, as these neurological effects have never been demonstrated following dermal exposure to ZPT, such effects are not expected to result in humans as a consequence of topical application of products containing ZPT.

2.3.8. Sub-chronic dermal toxicity

See point 2.3.7.

2.3.9. Sub-chronic inhalation toxicity

No data

2.3.10. Chronic toxicity

Ingredient based data

A two year feeding study was conducted by Larson (1958). Young Wistar rats in groups of ten males and ten females were fed diets containing ZPT at levels of 0, 2, 5, 10, 25 and 50 ppm. These levels correspond to approximately 0, 0.1, 0.25, 0.5, 1.25 and 2.5 mg/kg/day for adult animals. At the start of the study the corresponding levels were 0, 0.2, 0.5, 1.0, 2.5 and 5.0 mg/kg/day for the young rats. Survival in males was not adversely affected by ingestion of the compound, but the highest level caused hind-limb paralysis in some animals. None of the females on the 50 ppm diet lived beyond 80 weeks, and death was commonly preceded by paralysis. Mortality was also increased at 25 ppm, and paralysis occurred in some animals prior to death. In females, growth depression was marked at 50 ppm. Dietary concentrations of 2, 5 and 10 ppm appeared to have an accelerating effect on weight gain in both sexes, and males showed a comparable stimulation at 25 ppm. The no-effect level for males and females was 10 ppm (0.5 mg/kg/day). The only unusual finding upon termination of the study was an increase in neutrophil versus lymphocyte counts in males on the 50 ppm diet. Ratios of organ weights to

body weights did not differ significantly among the surviving groups at termination. Histopathologic examinations did not reveal any lesions that appeared to be attributable to the administration of ZPT. These observations included careful attention to retina, optic nerve, cerebral cortex, and other parts of the central and peripheral nervous systems. There were no significant differences in the rate of frequency of neoplasms between any of the groups.

Dermal

Ingredient based data

Since the highest dose level that was well tolerated in mouse pilot studies summarised previously was 0.1 ml of 10% ZPT, it was deemed suitable for use in the dermal carcinogenicity bioassay conducted by Patterson and Gargus (1979). ICR Swiss mice (730 animals) were selected at random and assigned to the following groups. Each received the noted treatment on a 6 cm² clipped area. No attempt was made to control ingestion of the applied material. The two dose levels represent approximately 20 and 100 mg/kg/day.

Table

Group	*Treatment*	*Number of mice*	
		male	*female*
1	Negative controls, no treatment	139	141
2	Vehicle controls 0.1 ml	75	75
3	Low dose, 0.1 ml vehicle (2 mg ZPT/application)	75	75
4	High dose, 0.1 ml vehicle (10 mg ZPT/application)	75	75

All animals were housed in individual hanging wire-mesh cages. Individual body weights were recorded initially and at monthly intervals. Observations were made daily for mortality and at each treatment period for evidence of systemic effect and skin lesions in the area of treatment. Treatment was continued for 18 months, at which time it was discontinued, and the mice were maintained until each group mortality reached 75%. The group was then necropsied. Only the males in the high-dose group experienced a mortality rate of 75% prior to the end of the study. For this group the average survival time was 409 days as compared to 492 days for the untreated males, which suggests a relationship to ZPT toxicity. However, neither gross examination of the animals and tissues, revealed any consistent lesion that would explain the reduced life span. The skin of all three treated groups exhibited changes consistent with exposure to a low-level chemical irritant.
There were no significant differences in the types or incidence of tumours or abnormal tissue masses between any of the groups that could be related to the administration of ZPT.

The chronic studies summarised above provide two essential pieces of information relevant to the safety evaluation of ZPT :

* 0.5 mg/kg/day (500 µg/kg/d) given orally to rats is a no-effect level
* no evidence of a carcinogenic response was seen when ZPT was applied topically (up to 100 mg/kg/d) or given orally (up to 5 mg/kg/d) in lifetime studies using mice and rats.

2.4. Irritation & corrosivity

2.4.1. Irritation (skin)

Irritation studies have been conducted with marketed shampoos containing ZPT in humans.

A study evaluated the effect of ZPT in a marketed shampoo base on human skin pigmentation at sub irritating levels. Product was applied daily at 0.2, 0.4, and 2.0% under non-occluded dressings to each of eight Caucasians and eight black males for 64 consecutive days. Under the experimental conditions used the cream and lotion shampoos did not produce any skin irritation, nor did they change the skin pigmentation level in Caucasian or black skin.

Ref. : 37

A case report described a reaction by a patient to a shampoo containing 2% ZPT. The patient had had a similar reaction after using a hair cream with a lower level seven years before. Another report described a case of eczema of the scalp and face after using a shampoo containing 2% ZPT for a short period.

Ref. : 4, 23

Conclusion
The presence of ZPT in cosmetic formulations did not impact upon the low irritation potential of the formulations tested.

2.4.2. Irritation (mucous membranes)

The eye irritation potential of ZPT has been evaluated in a number of product types :

* Instillation of a soap solution containing 0.25% ZPT to rabbit eyes produced slight transient irritation with the peak effect occurring during the first 4 hours and having disappeared completely in 2-4 days.

* In another study, undiluted and diluted solutions of shampoo with or without ZPT (2%) were tested. Undiluted solutions produced extensive damage to the eyes of rabbits which was characterised by opalescence of the entire cornea, severe iritis and marked conjunctivitis. In all cases, rinsing was particularly effective in alleviating the condition with very slight to moderate conjunctivitis being observed. In all rinsed cases, damage had cleared by the third day whereas in unrinsed eyes the condition had not cleared by day 42. Dilution of these test solutions to 10% also reduced the ocular irritation and in all cases the condition was cleared by day 7. Again, rinsing was effective in alleviating the condition. No significant differences were observed between the control and the test animals in this study.
Repetition of the above study in monkeys with no rinsing produced superficial damage to the corneal epithelium and/or slight conjunctival irritation when the 2% ZPT shampoo was instilled undiluted. Instillation of the shampoo formulation diluted to 10% (0.2% ZPT) resulted in no ocular irritation.

Conclusion
The irritation potential of shampoo in rabbit eyes was not increased by the incorporation of ZPT.

Ref. : 61

2.5. Sensitisation

Ingredient based data

ZPT was evaluated for its potential to induce contact hypersensitivity to guinea pigs. Using the procedure of Buehler (1965) to detect contact hypersensitivity, 40 animals were exposed to a 50% aqueous slurry of ZPT. No reactions indicative of contact hypersensitivity were seen in any of the animals at challenge.

Ref. : 25

The work by the Danish Contact Dermatitis Group was described in which ZPT (1%) was added to the European Standard Patch Test series. 1652 consecutive dermatitis patients were tested. Only three positive reactions were found. The authors state that in only one of these was the ZPT reaction interpreted with certainty as being of present relevance. They also point out the wide use of ZPT in "shampoos, hair creams and cosmetics". Bearing this in mind, and recalling that all the subjects tested had known skin problems, this is a remarkably low incidence of reactions, and underline the very low risk from ZPT in the sensitisation area.

Ref. : 4

A multi-centre investigation was conducted in France in order to evaluate the risk of sensitisation by a number of preservatives. 465 subjects were tested. They were suffering from an eczema for which the anecdotal circumstances pointed to an allergy to cosmetics, medicine, industrial products or clothing accessories. Only two patients (0.4%) gave positive patch tests to ZPT.

Ref. : 38*

Product based data

Many sensitisation studies have been conducted with marketed shampoos containing ZPT, using both animals and humans. A number of human repeat insult patch tests (HRIPT) have been conducted employing over 1000 human volunteers. The irritation potential was also investigated in all HRIPTs.

In general, whether injected intradermally or applied topically, and regardless of the species, ZPT has been repeatedly demonstrated to be rare or even a non-allergenic.

A 0.1% solution of the ZPT (1 % ZPT) soap was injected intracutaneously into depilated guinea pig skin at an initial dose of 0.05 ml and nine subsequent doses of 0.1 ml on alternate weekdays. A single challenge dose of 0.05 ml was injected two weeks later. There was no evidence of sensitisation.

Ref. : 61

Two separate closed-patch test studies on human volunteers were conducted. A 1% aqueous solution of shampoo containing 2% ZPT was used. The test solution was placed on the upper arm of the subjects and occluded. Nine serial applications were made on alternate weekdays for three weeks, followed by challenge two weeks later. Challenge patches with the same concentration of test material were placed on both the original site of insult and on an alternate site on the opposite arm to distinguish between skin fatigue and sensitisation.

Reactions were scored at both 48 and 96 hours. One subject gave papular reaction at 48 hours, which was scored negative at 96 hours. Unfortunately no follow-up was done with individual ingredients, so it is impossible to determine whether indeed the subject was sensitised, and if so, what the offending material was. The remaining subjects gave only a transient erythematous response indicative of irritation.

Ref. : 61

Cream and lotion shampoo products were tested in two separate HRIPT's. Both studies were conducted according to the modified Draize procedure described above, in which 0.25% shampoo was patched. No sensitisation was detected in the 82 subjects exposed to the cream nor in the 78 subjects exposed to the lotion. The only responses noted were transient primary irritation in some subjects.

Ref. : 26, 65

A hair dressing cream containing 0.5% ZPT was used to patch test more than 100 women for five months. A minimum of 80% of the subjects were patched weekly for 20 consecutive weeks. Patches were left in place for 48 hours and sites graded 72 hours after removal. Throughout the entire test program, no instances of any skin reactions were observed. Thus, it was concluded that the hairdressing product possessed an extremely low index of sensitisation in humans.

Ref. : 46*

Marketing experience with a commercially available formulation has conclusively demonstrated that ZPT is, at worst a very weak sensitiser. Few reports of sensitisation have appeared in the literature.

Ref. : 4, 17, 23, 40

Summary
When tested alone, ZPT has a low potential to induce contact hypersensitivity. When tested as part of a cosmetic formulation, ZPT has a low potential to induce contact hypersensitivity.

Ref. : SCCNFP 1 to 5

2.6. Reproductive toxicity

Several teratology/reproduction studies have been conducted using rats and rabbits, in which ZPT was either applied topically or given orally. Topical application (with ingestion during grooming) of levels up to 15 mg/kg/day did not adversely affect reproduction in rats. When pregnant rats were gavaged with 15 mg/kg/day of ZPT, there was an increase in the incidence of forked and fused ribs in the neonates. A dose level of 2.5 mg/kg/day given orally is a no-effect level for teratogenicity/embryotoxicity. No material toxicity was observed in these studies.

Teratology data are summarised in the table below, followed by a brief description of each of the studies.

Table : Summary of Teratogenicity Studies

Species	*Route of administration*	*Dose levels (mg/kg)*	*Teratology findings*	*Ref.*
Rat	Oral	7.5 15.0	7.5 – none 15.0 – increased incidence of fused or forked ribs	24
Rat	Oral	7.5 15.0	7.5 – none 15.0 – increased incidence of fused or forked ribs	43
Rat	Topical with ingestion of applied material	2.5 7.5 15.0	2.5 – none 7.5 – none 15.0 - none	43
Rat	Topical	2.5 7.5 15.0	2.5 – none 7.5 – none 15.0 - none	43
Rabbit	Oral	5.0 10.0 20.0	5.0 - fatal to 6/15 dams, no teratogenic effects 10.0 - fatal to 10/15 dams, no teratogenic effects 20.0 - fatal to 15/15 dams	43
Rabbit	Oral	1.0 2.5 5.0	1.0 – none 2.5 – none 5.0 - none	43
Rabbit	topical	25.0 50.0 100.0	25.0 – none 50.0 – none 100.0 - none	43

Oral, Ingredient based data

In the teratology study conducted by Haley et al (1971) groups of 19, 16, and 20 albino rats were administered dose levels of 0, 7.51 or 15.0 mg/kg/day, respectively, of ZPT for the sixth through the fifteenth day of gestation. The material was dosed as a solution in corn oil by oral intubation. All animals were allowed food and water ad libitum. Maternal body weights were depressed in the groups given ZPT. The mean weight gain per animal for the control group was 132 mg, for the group receiving 7.5 mg/kg, 69 g; and for the group receiving 15.0 mg/kg, 89 g. An increased incidence of skeletal abnormalities, particularly fused and forked ribs, was seen in the foetuses in the higher dose group, but not in the group receiving 7.5 mg/kg/day.

Nolen and Dierckman (1979) in a series of studies evaluated the embryotoxic/teratogenic effects of ZPT in rats and rabbits. Initially they confirmed the report by Haley et al (1971) in that pregnant rats dosed orally with 15 mg/kg/day produced litters with an increased incidence of skeletal abnormalities. They also confirmed that 7.5 mg/kg day did not cause a statistically significant increase in the number of foetal abnormalities.

ZPT administered orally to pregnant rabbits from Day 6 through Day 18 of pregnancy was lethal to 6/15 at the 5 mg/kg level, 10/15 at the 19 mg/kg level and 15/15 at the 20 mg/kg level.

The surviving animals lost weight and had significantly higher incidences of embryonic resorption. However, there was no evidence of teratogenicity. In another experiment, rabbits were dosed orally with 1, 2.5, or 5 mg/kg of ZPT. Animals receiving 5 mg/kg lost a significant amount of weight, but none died. In addition, the number of resorptions was significantly increased compared to the water control. Dams dosed with 2.5 mg/kg ZPT gained less weight than controls and had a higher incidence of resorptions, neither observation being statistically significant, while the data from dams treated with 1 mg/kg were similar to those of the control. None of the ZPT doses had any adverse effects on foetal development.

Thus, 2.5 mg/kg/day is a no-effect level for orally administered ZPT in teratology studies.

Dermal, Ingredient based data

No deleterious effects were seen in rabbits treated topically with 25, 50, or 100 mg ZPT/kg/d with oral ingestion controlled by a leather harness, and as in the other rabbit studies, no teratogenic effects were observed in this study (Nolen and Dierckman (1979)).

In a separate study using rats, Nolen and Dierckman (1979) topically applied a 48% aqueous slurry of ZPT to three groups of 10 animals at levels of 2.5, 7.5, and 15 mg/kg/day. The animals were dosed from eight weeks before mating until Day 15 of gestation. No attempt was made to control ingestion during grooming in that the material was not washed off, and additional application were made over the previous treatment. Three other groups of rats were treated at the same dose levels, but ingestion of the ZPT was prevented by means of plastic domes glued to their backs. The animals in this portion of the study were treated from Day 6 through Day 15 of gestation. In the rat reproduction portion of the study, ZPT produced no adverse effects on growth, pathology, or conception in the parents, or on viability, post-weaning growth, or pathology in the neonates. Ingestion of the material during grooming did cause hind-limb paralysis in 2/10 dams dosed at 7.5 mg/kg/day and in 5/10 dams dosed at 15 mg/kg day. There was no evidence of any adverse effects in any group in either the dams or foetuses when ingestion was prevented by the plastic dome.

No teratogenic or adverse effects on reproduction have been seen when the material is applied topically to rats and rabbits at levels up to 15 and 100 mg ZPT/kg/day respectively (highest doses tested).

Product based data

Teratology studies have been conducted using rabbits and pigs in which ZPT was incorporated into a product base and applied topically. Jordan and Borzelleca (1975) studied the effects of 1%, 2% or 6% ZPT applied as part of a shampoo formulation to the backs of pregnant Yorkshire swine at levels equivalent to 50, 100, or 300 mg/kg/day. Product was applied from day 12 through day 36 of gestation. There was no evidence of embryotoxicity nor teratogenic effects in the foetuses.

In a study reported by Wedig et al (1976), Yorkshire pigs were again used as the test species. In this test, a 50% (w/v) suspension of ZPT in Aquafor Cream (commercial product) was applied to a 380 cm' area of the backs of the animals. Eight dose sites were used in rotation to prevent

irritation at the dosing area. An untreated group and a group treated with Aquafor Cream without ZPT were used as controls. Dose levels of ZPT were 30, 100, and 400 mg/kg/day. Material was left on the skin for eight hours/day from the eighth through the thirty-second day of gestation. During the treatment period each animal was individually confined in such a manner as to prevent oral ingestion of the test materials. Slight erythema was observed in some animals during the dose administration period, but all lesions were reversible and were not apparent at sacrifice (Day 100). No signs of systemic toxicity were observed in any of the animals. Maternal body weights were not depressed by administration of ZPT. No evidence of teratogenic effects was observed in the foetuses from the ZPT-treated animals either grossly following examination of internal organs or upon skeletal examination.

Nolen et al (1975) have reported the results of a percutaneous teratology study of ZPT in rabbits. A lotion shampoo containing 2% ZPT was applied for two hours each day at either I or 2.5 g/kg (20 or 50 mg/kg of ZPT) from the seventh to the eighteenth day of gestation to groups of 15 rabbits. A third and fourth group of animals received either no treatment or the shampoo base without ZPT. These were control groups. Oral ingestion was prevented by harnessing the animals and cleaning the cages. ZPT had no effect on maternal weight gains and was not teratogenic under these conditions.

No teratogenic effects were seen in rabbits topically treated from the seventh to the eighteenth day of gestation with shampoo containing up to 50 mg/kg ZPT. Neither were effects seen in pigs topically treated from the eighth to the thirty sixth day of gestation with a shampoo containing up to 300 mg/kg ZPT.

In summary

* 2.5 mg/kg/d administered orally to rats is a no effect level for teratological effects
* no reproductive effects have been observed when ZPT was applied topically to rats and rabbits at levels up to 15 and 100 mg ZPT/kg/d respectively (highest doses tested) and ingestion of the test material was controlled.
* no reproductive or teratogenic effects have been observed in rabbits and pigs following topical application of shampoo formulations containing 50 and 400 mg ZPT/kg/d respectively.

2.7. Toxicokinetics (incl. Percutaneous Absorption)

Ingredient based data

Deposition and absorption

Parran (1965) showed that particles of ZPT were deposited on the scalp from shampoos. He stated that the particles could not be removed by vigorous and prolonged rinsing with just water, but gradually decreased in number with some still detectable two to three days after shampooing. Okamoto et al (1967) determined the substantivity of ZPT to the skin of rats and rabbits using shampoos with ^{35}S-ZPT for rats and ^{65}Zn-ZPT for rabbits. Substantivity to clipped rat skin following shampoos of one and five minutes with a 1.82% ZPT shampoo followed by rinsing was 9.2 and 11.6 µg/cm^2, respectively. These data agree with those reported by Snyder et al (1965), Okumura et al (1975) and Black et al (1975).

Okumura et al (1975) found the adsorption of ^{35}S-ZPT from a 1 % ZPT shampoo to be 0.1 μg/cm^2 for mice and about 10.1 μg/cm^2 for rats. The data for mice were derived from counting skin samples, whereas the rat data were estimated from counts of successive tape strippings. The difference in the amounts adsorbed between two similar animals is much larger than would be expected, but could be partially accounted for by differences in experimental procedures.

Black et al (1975) determined the deposition of ^{35}S-ZPT from shampoo on rat skin as a function of concentration in shampoo, duration of contact with the skin, pH of shampoo, and nature of the detergent in the shampoo formulation. In experiments with from 0.1 % to 2.0% ZPT in shampoo, the deposition increased from 0.03 to 6.44 p.g/cm^2. The duration of contact and pH of the shampoo did not affect deposition, but different detergent compositions did. These results agree with those reported previously by Snyder et al (1965) and Parran (1965).

Rutherford and Black (1969) used autoradiography to study the localisation of ZPT in guinea pig skin. They found clear evidence that ZPT particles are adsorbed on skin and hair and that solubilised ZPT enters hair follicles. A quantitative estimate of the amount of ^{35}S-ZPT adsorbed on skin was made by counting 25-um serial sections of guinea pig skin cut parallel to the surface. The adsorbed ZPT was found to be 1.4 to 3.6 μg/cm^2.

The data from the various studies summarised above suggest that deposition on animal skin is equal to approximately 1 % of the applied ZPT, and is therefore concentration dependent, but independent of contact times from 1 to 32 minutes.

Gibson and Calvin (1978) used rhesus monkeys to study absorption from a three-hour application of 2% ^{35} S-ZPT to a 10 cm^2 area of the abdomen. They found that 0.03-0.04 of the administered dose was absorbed. The absorption was increased approximately 10x using abraded or stripped skin. As in previously cited work, the ^{35}S was excreted in the urine. In separate monkey studies using scalp exposure to ^{14}C-ZPT, about 3.4% of the ZPT was absorbed whether a 3- or 72-hour exposure was used, confirming the data of Howes and Black (1975). Blood levels, however, were below the limit of detectability (1 ppb). These differences in percentage absorption may be explained by factors such as vehicle differences, differences in skin site and therefore the presence/absence of hair follicles.

Spiker and Ciuchta (1980) have conducted a rabbit study in which they made dermal application of a shampoo containing 0.75% ZPT twice daily for four days. They found that surfactant irritation had occurred, but no ZPT penetration as measured by whole-blood zinc levels. They did report, however, that 3.75% ZPT in 28% ammonium lauryl sulfate produced large increases in whole blood zinc levels with reductions in plasma zinc 6 hours after a 24-hour exposure. They attributed these changes to the chelating nature of the pyrithione molecule.

Distribution

Distribution of ZPT after intravenous, oral and topical administration has been studied by Okamoto et al (1967), Klaassen, (1976), Gibson et al (1982) and Ziller (1977). Various tissue concentrations of labelled material were followed for periods of 5 min. to 72 hr. In general, these concentrations were less than that found in the blood, indicating that

neither ZPT nor any metabolite is selectively taken up by any organ. Transient elevations of label in the liver and kidney were noted by Gibson (1977), suggestive of liver metabolism and renal excretion.

Metabolism

Much of the literature to date concerning the metabolism of pyrithiones refers to compounds other than the zinc chelate. The biological fate of these materials along with ZPT has been studied in different animal species, and several metabolites have been reported. Evans et al (1975) have shown that many of these metabolites are intermediates or end products in the photo-oxidation of pyrithiones. Considerable work (described below) has been done to define excretory rates and the nature of the metabolites produced by administration of ^{14}C-ZPT to rats, rabbits, dogs, and monkeys. In these studies, extreme care was taken to protect the dosing suspensions and biological samples from photo-oxidation or chemical oxidation, and metabolite separations were conducted under conditions that minimised the possibility of nonenzymatic alteration. All animal species were dosed with ZPT in the same dose vehicle, at the same dose level (1 mg/kg), and by the same dose route (oral intubation). The urinary metabolites were separated by high-performance liquid chromatography and subsequently identified by Jeffcoat et al (1980) by spectrophotometric techniques and comparison with the authentic materials. ZPT was biotransformed by all four species in qualitatively similar ways. Two major metabolites, 2-pyridinethiol-S-glucuronide and 2-pyridinethiol-N-oxide-S-glucuronide were found. The latter was the more abundant in each case.
Significant quantities of 2-pyridinethiol-N-oxide-S-glucuronide were also excreted by all species except the rat. In contrast to previously reported work, (Min et al (1970), Kabacoff et al (1971), Howlett and Van Abbe (1975), Adams et al (1976) and Wedig et al (1978a)), the data show that pyridine-N-oxide-2-sulfonic acid, the 2,2' disulfide of pyridine, and 2,2disulfide of pyridine, are not major urinary metabolites in any of the species studied.

Work by Wedig et al (1978a), support the findings of Jeffcoat et al (1980) in that they reported 2-pyridinethiol-N-oxide as a minor urinary metabolite and the S-glucuronides of 2-pyridinethiol-N-oxide as major metabolites for rats dosed orally with ^{14}C-ZPT.

Few reports in the literature describe ZPT metabolites in the systemic circulation. Adams et al (1976) studied the clearance of ZPT metabolites from the plasma of swine after intravenous dosing with ^{14}C-ZPT and described the clearance as biphasic. However, the chemical species that contributed to the circulating radioactivity were not identified.

Identification of the major serum metabolite comes from work by Gibson et al (1982). Gibson et al (1982) investigated the metabolites of ZPT in the systemic circulation of rabbits, rats, monkeys, and dogs after they were dosed with 1 mg ^{14}C-ZPT/kg of body weight by stomach tube. The clearance of radioactivity from the blood of all four species was similar and followed a biphasic kinetic pattern. The blood radioactivity concentration reached maxima at two different times. The first maximum occurred between one and eight hours after dosing and was caused by the rapid formation and elimination of several polar metabolites. A second, broad maximum resulted from 2-(methylsulfonyl) pyridine (MSP). This metabolite had an apparent half-life of a day or more, and in the rat, it was the only predominant serum metabolite 16 hr. after dosing.

Since MSP was the only major serum metabolite likely to accumulate, infusion studies were conducted (Gibson et al (1982)) to see if MSP would produce paralysis. Although the duration of infusion and the serum concentrations of MSP attained were greater than those predicted to produce paralysis from the ZPT feeding study, no paralysis was observed.
The lack of significant differences among the species tested by Jeffcoat et al (1980) and Gibson et al (1982) with regard to ZPT metabolism suggests that human metabolism of ZPT is likely to be similar.

Parekh et al (1970) injected ^{35}S-NaPT intravenously into rats and detected small amounts of labelled material in the bile. Thin layer chromatography (TLC) was used to identify the major urinary metabolite as pyridine-N-oxide-2-2'-disulfide and another metabolite as pyridine-N-oxide sulfonic acid. TLC was also used by Min et al (1970) to identify pyridineN-oxide sulfonic acid as a metabolite in the urine of rats treated topically with ^{35}S-NaPT. Over the first 24 hr. after application, 2.1 % of the applied material was excreted. Of this, 95% was in the form of pyridine-N-oxide sulfonic acid. Another urinary metabolite that has been reported by Kabacoff et al (1971) is the glucuronide conjugate of pyridinethione, which was determined to be the major metabolite in the urine of rats dosed orally and rabbits dosed intravenously with NaPT.

Howlett and VanAbbe (1975) presented a detailed report on the absorption of ^{35}S-NaPT through the skin of rabbits. The data suggest rapid urinary excretion of ^{35}S labelled compounds with no evidence for selective uptake into any organ. Enterohepatic recirculation was suggested by the data relating to bile, gut, and faecal levels of ^{35}S. Metabolite identification work indicated that the principal urinary metabolite was pyridineN-oxide-2-sulfonic acid.

The major urinary metabolite of ZPT and the magnesium sulfate adduct of 2,2' (pyridineN-oxide)-disulfide (MDS) after intravenous injection in swine was identified by Adams et al (1976) as pyridine-N-oxide sulfonic acid, and pyridine-N-oxide disulfide for NaPT.

In another study, Wedig et al (1978) administered either ZPT, NPT, or MDS intravenously or by dermal application to female Yorkshire swine. The major metabolite in urine after intravenous dosing of ZPT, NaPT, and MDS was 2-pyridinethiol-N-oxide-S-glucuronide, and a minor metabolite was 2-pyridinethiol-S-glucuronide. After dermal application, the metabolites were 2,2'-pyridine disulfide and 2 (pyridine-N-oxide)-sulfonic acid.

Wedig et al (1984) have confirmed that 2-Methylsulfonylpyridine (2-MSP) can be detected at very low levels in the systemic circulation of humans involved in the ZPT manufacturing process. This confirms that the terminal pyrithione metabolite in plasma is identical among rat, rabbit, dog, monkey and man. (It should be noted that these workers, in contact with the manufacturing process for 2-13 years, were all in excellent health).

Excretion

ZPT is rapidly and extensively absorbed from the gastrointestinal tract after oral dosing. Ziller (1977) showed that ZPT, labelled with ^{35}S, fed orally to rats at 25-35 mg/kg, resulted in 65-70% of the doses being excreted in the urine in 72 hr with 2-17% in faeces. Overall recovery of ^{35}S was 90-92%, of which 5% was in the animal at 72 hr. A small amount of labelled material was

excreted in the bile (10-15%) as shown by cannulation studies, which suggest enterohepatic recirculation, since faecal excretion is usually lower than this level.

Ziller (1977) also dosed a monkey with 10 mg/kg of ZPT and found that 90% of the dose was excreted in the urine and 1 % in the faeces. Less than 1 % remained in the carcass at 72 hr. Overall recovery was 91% of dose. Jeffcoat et al (1980) dosed rats, rabbits, monkeys, and dogs with ^{14}C-labelled ZPT at a dose level of 1 mg/kg. The radioactivity excreted in the urine accounted for 75% of the dose in rabbits, 82% in rats, 95% in monkeys, and 94% in dogs. The majority of the ^{14}C was eliminated within 24 hr. All species excreted only a small percentage of the dose in their faeces.

Okamoto et al (1967) reported that orally administered ZPT, doubly labelled with ^{65}Zn and ^{35}S, resulted in a wide tissue distribution of ^{35}S with its eventual excretion in the urine. The ^{65}Zn was excreted in the faeces, suggesting that ZPT decomposed in the stomach. This was supported by the work of Klaassen (1976) who administered ^{14}C- or ^{65}Zn-labelled ZPT to rabbits by the intravenous, oral, and dermal routes. He studied the tissue levels of the isotopes six hours after dosing. The data show that the zinc and organic portions of the molecule distribute independently as the $^{65}Zn/^{14}C$ ratios vary from organ to organ. It was concluded that the zinc portion of the molecule equilibrated with the body zinc pool and the organic portion of the molecule was cleared primarily through the kidneys.

Summary

* percutaneous absorption of ZPT varies from approximately 0.03 to 3.4%
* the distribution of radioactivity in tissues after oral administration of labelled ZPT showed that the radioactivity rapidly disappeared from the blood, and the primary route of excretion was via the urine. The residual radioactivity was low (4.5% of dose), ZPT was distributed throughout the body, and was not concentrated in any particular tissue.
* all animal species investigated (rat, rabbit, dog, and monkey) biotransformed ZPT in qualitatively similar ways. This similarity with regard to ZPT metabolism suggests that human metabolism is likely to be similar. This has been confirmed by Wedig et al (1984).

Product Based Data

A clinical pharmacokinetic study has investigated deposition, absorption and excretion of ^{14}C-radiolabelled ZPT resulting from the use of a ZPT containing shampoo alone (1 % ZPT) and in combination with a ZPT containing leave on hair tonic (0.1% ZPT) (see Annex I). This study demonstrated that systemic loading of ZPT was increased significantly less than could be expected from the corresponding skin deposition in those subjects using the shampoo/tonic combination compared with those using the shampoo alone. Additionally, absorption of ZPT in patients with compromised scalps was not found to be statistically different to normal scalps patients.

Deposition, absorption and excretion parameters were measured in 20 volunteers (10 patients using ZPT containing shampoo alone (Group A) and 10 using the ZPT containing shampoo and ZPT containing tonic combination (Group B)) over a 4 day treatment period. Each treatment

group was comprised of 5 patients with healthy scalps and 5 patients with compromised scalps with either severe dandruff or seborrheic dermatitis. All patients used 10 g of shampoo per day and those in Group B also used 4 g of tonic per day during the 4 day treatment period.

Measurements of ZPT deposition and excretion were made by analysis of clipped hair, tape stripping areas of the scalp and hands and urinalysis respectively. Previously, preclinical studies have demonstrated that >_ 90% of absorbed ZPT is excreted in the urine within 24 hours, thus for the purposes of this study the level of ZPT excreted was taken to represent the level of ZPT absorbed (i.e. systemic dose).

Mean results are shown in the following tables.

Table : Mean ^{14}C-ZPT Skin Deposition Measurements (Scalp and Hands)

Day[#]	**1% ^{14}C-ZPT Shampoo**		**1 % ^{14}C-ZPT Shampoo + 0.1% ^{14}C -ZPT Tonic**	
	LSM amount of ZPT deposited (µg /cm^2)	Estimated total ZPT deposited (µg)	LSM amount of ZPT deposited (µg/cm²)	Estimated total ZPT deposited (µg)
1	0.39	288.00	0.88	644.93
2	0.43	317.60	0.96	693.19
4	0.50	363.30	1.33	967.60
5	0.20	146.80	0.40	296.31

[#] Day 3 deposition measurements not recorded as a practical consideration to study participants to avoid excess hair removal
LSM = Least Squares Mean

Table : Mean ^{14}C-ZPT Systemic Load

Day	**1% ^{14}C-ZPT Shampoo**		**1 % ^{14}C-ZPT Shampoo + 0.1% ^{14}C -ZPT Tonic**	
	LSM systemic load (µg /kg/d)[#]	SEM	LSM systemic load (µg /kg/d)[#]	SEM
1	1.02	0.14	1.39	0.14
2	2.54	0.33	3.31	0.33
3	2.73	0.32	3.32	0.32
4	2.76	0.35	3.43	0.35
5	1.96	0.32	2.29	0.32

LSM = Least Squares Mean
SEM = Standard Error of the Mean
[#] Average body weight per group used for calculation of µg/kg/d values

Table : Comparison Of Mean ^{14}C-ZPT Absorption in Normal And Compromised Scalp Subjects

Day#	LSM amount of ZPT absorbed (% of dose deposited)				Statistical analysis – p-values	
	1% ^{14}C-ZPT Shampoo		1 % ^{14}C-ZPT Shampoo + 0.1% ^{14}C -ZPT Tonic			
	Normal scalp	Compromised scalp	Normal scalp	Compromised scalp	ASF	ASF*TRT
1	25.39	46.48	20.58	20.84	0.24	0.25
2	68.08	57.26	49.75	47.57	0.58	0.71
4	57.51	52.67	43.85	27.39	0.39	0.64

# Day 3 deposition measurements not recorded as a practical consideration to study participants to avoid excess hair removal
LSM = Least Squares Mean
ASF = Adherent Scalp Flaking (normal versus compromised scalp) TRT = Treatment group

Analysis of the dermal deposition data indicated :

* ZPT deposition on the hands between the treatment groups A and B was not significantly difference throughout the study except on day 2
* ZPT deposition on the scalp between the treatment groups A and B was statistically different with deposition in Group B being significantly higher than group A
* ZPT deposition on the hands was determined to be approximately half the level deposited on the scalp
* ZPT deposition on the hair between the treatment groups A and B was statistically different with deposition on hair in Group A being half the level of Group B

Analysis of individual subject absorption data indicated that individuals with compromised scalps demonstrated no greater absorption than individuals with normal scalps.

Analysis of the urinary excretion curves indicates that steady state conditions were reached within the 4 day treatment period of this study. Statistical analysis indicated that the amount of ZPT excreted in the urine (indicative of systemic exposure) was significantly higher in the shampoo + tonic group (B) compared with the shampoo only group (A) throughout the study. However the increase was less than what would have been expected from the increase in skin deposition. This suggests a rate limiting mechanism exists for the absorption of ZPT across the skin.

2.8. Mutagenicity/Genotoxicity

The mutagenic potential of ZPT was evaluated in the *Salmonella*/mammalian microsome plate incorporation mutagenicity assay (Ames test). ZPT was negative in the five tester strains (TA98, TA100, TA1 353, TA1 537 and TA1538) in the presence and absence of rat liver microsomal

enzymes (S9 fraction) when assayed at concentrations ranging between 10 and 333 µg/plate and between 0.03 and 33 .1g/plate respectively.

Ref. : 60

The mutagenic potential of ZPT was evaluated in the CHO/HGPRT gene mutation assay. No significant increases in mutant frequencies were seen in the presence and absence of rat liver microsomal enzymes (S9 fraction). In each case, the highest concentrations reduced cellular viability by 83% and 85% respectively.

Ref. : 60

The clastogenic potential of ZPT was evaluated using the mouse micronucleus test. ZPT did not induce increased frequencies of micronuclei in mouse bone marrow cells when tested at the maximally tolerated dose (44 mg/kg).

Ref. : 60

ZPT was tested for the induction of unscheduled DNA synthesis in cultured human fibroblasts (WI-38 cells) with and without exogenous metabolic activation by a microsomal enzyme (S-9) preparation from Aroclor-induced rat liver. Unscheduled DNA synthesis was monitored by the incorporation of 3H-thymidine into the nuclei of growth-arrested WI-38 cells. The incorporation of radioisotope was determined by light microscope autoradiography. No evidence for unscheduled DNA induction by the test substance was found. At the higher doses of the test substance, DNA replication in S-phase cells was inhibited.

Ref. : 58

Conclusion
ZPT has shown no mutagenic effect in any of the in vitro and in vivo studies conducted.

2.9. Carcinogenicity

No data

2.10. Special investigations

Market experience

ZPT has been used as an anti-dandruff active in shampoo formulations at levels of 1.0 and 2.0% since the 1940's. During this time there has been little evidence of any serious adverse effects from this usage, and those few effects that have been recorded are limited to eye and skin irritation as can be expected for surfactant-based formulations.
The effective use of shampoos containing this ingredient involves regular (2-3 times a week at least) usage.

Recent tracking of consumer marketplace complaints continue to indicate that ZPT containing shampoos have a very similar, low problem incidence profile compared to conventional shampoos which do not contain the material.

2.11. Safety Evaluation

NOT APPLICABLE

2.12. Conclusion

The use of Zinc pyrithione (ZPT) is authorized as a preservative in rinse-off cosmetic products up to an maximum concentration of 0.5 %. For "other uses" preferably as an antidandruff agent ZPT is used for a long time, more than 60 years in concentrations up to 1-2 % in appropriate cosmetic products. Thus there is an immense number of practical/epidemiological experiences.

Moreover there is a long list of controlled toxicological and functional investigations published in the scientific literature. It could be demonstrated that the acute as well as the subchronic toxicity is moderate to low, both ZPT alone or incorporated in market formulations, and also in animal experiments or after practical application to humans. Thus the scientific evaluation of the submission, the results of these investigations on ZPT have been separated as to (i) ingredient based data, (ii) product based data and, where applicable, to the mode of application.

As to probable neurotoxicological properties of ZPT the results of investigations in several species can be summarized as follows:

In chronic toxicity experiments it was shown that an oral application of 500 µg/kg/d applied over (~ 18 m) can be regarded as NOAEL. No evidence of a carcinogenic response was seen when ZPT was applied topically up to 100 mg/kg/d or given orally up to 5 mg/kg/d in lifetime studies.

The presence of ZPT did not impact upon the low irritation potential of the cosmetic formulations tested. The same observation was valid for a shampoo formulation investigated in a mucous membranes test. The appropriate experiments showed that ZPT alone as well as part of cosmetic formulations had a low potential to induce contact hypersensitivity.

In teratological studies 2.5 mg/kg/day applied orally to rats was the NOAEL maternally, no reproductive effects were observed in rabbits and rats when ZPT was topically administered up to 400 mg/kg/day.

Toxicokinetic investigations revealed :

* percutaneous absorption of ZPT varies from approximately 0.03 to 3.4%
* the distribution of radioactivity in tissues after oral administration of labelled ZPT showed that the radioactivity rapidly disappeared from the blood, and the primary route of excretion was via the urine. The residual radioactivity was low (4.5% of dose), ZPT was distributed throughout the body, and was not concentrated in any particular tissue.
* all animal species investigated (rat, rabbit, dog, and monkey) biotransformed ZPT in qualitatively similar ways. This similarity with regard to ZPT metabolism suggests that human metabolism is likely to be similar. This has been confirmed by Wedig et al (1984).

In mutagenicity/genotoxicity studies ZPT has shown no effects in any of the in vitro and/or in vivo studies conducted.

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3. Opinion

The SCCNFP is of the opinion that zinc pyrithione does not pose a health risk when used :

* for non-preservative purposes in cosmetic rinse-off and leave-on hair care products at a maximum concentration of 1.0 % and 0.1 %, respectively;

or,

* for preservative purposes in cosmetic rinse-off hair care products at a maximum concentration of 1.0 %.

Zinc pyrithione should not be used in products for oral hygiene.