JERZY ŁUKASIAK[1)*], ZYGMUNT JAMRÓGIEWICZ[1)],
DOROTA JACHOWSKA[1)], WOJCIECH CZARNOWSKI[2)],
MARIA HRABOWSKA[3)], MAGDALENA PROKOPOWICZ[*)],
BOGDAN FALKIEWICZ[4)5)]

Absorption and distribution of orally administered siloxanes in rat organs

RAPID COMMUNICATION

Summary — Male „Wistar" rats, each *ca.* 200 g, were fed, each *ca.* 50 g/day, with (*i*) a 95% of granulated LSM + 5% of OM-300 polydimethylsiloxane (PDMS) oil (viscosity about 300 cSt) fodder and (*ii*) a (95:5 w/w) LSM — polydimethylcyclosiloxane (cPDMS) oil (*i.e.*, a (1:1) hexamethyltricyclosiloxane (D_3) — octamethyltetracyclosiloxane (D_4) mixture) fodder. Absorption from the alimentary tract and distribution of siloxanes in blood, brain, kidneys, liver and spleen was studied over a 24-hour period in the animals given the first lot of fodder and killed by one in 1, 5 and 24 h. Accumulation and toxic effects of siloxanes were studied in blood, brain, kidneys, liver and spleen in the animals killed after 12 days (Table 1). Silicones were extracted with CCl_4 and determined by recording ^1H NMR spectra on a Tesla Brno BS-587A 80-MHz spectrometer. In groups (*i*) and (*ii*), the mean siloxane concentrations in the blood after 12 days were 26±14 and 70±97 μg/mL, resp. In the specific organs, siloxanes differed only insignificantly between group (*i*) and (*ii*), except for brain where group (*i*) exceeded group (*ii*). In two rats, one given (*a*) LSM + 1 g OM-300 and the other given (*b*) LSM + 1 g cPDMS, the 24 h urine and feces contained (*a*) 300 μg and 800 mg silicones, resp., and (*b*) 10—30 μg and 400 mg, resp. PDMS are preferentially absorbed by the brain and kidneys; cPDMS remain in the circulatory system and partly in kidneys. The internal organs showed no pathological changes attributable to siloxanes.

Key words: polydimethylcyclosiloxanes, intestinal absorption, polydimethylsiloxanes.

Siloxanes constitute a mixture of mainly linear poly(dimethylsiloxanes) (PDMS) of varying molecular weights and poly(dimethylcyclosiloxanes) (cPDMS) are their common contaminants. As simethicone or dimethicone, they are used in pharmacy as components of oral preparations. An increasing use of siloxanes is also noted in food production technologies [1, 2]. The generally accepted opinion that, when taken orally, PDMS of higher molecular weights are not absorbed, was one of the main criteria in establishing the oral PDMS Acceptable Daily Intake of up to 1.5 mg/kg body weight. The highest permissible concentration of PDMS in foodstuffs has been defined as 10 mg/kg final product [1, 2]. Siloxanes of viscosities exceeding 50 cSt (centistoke, 10^{-6} m^2/sec) are permitted for internal use only [1, 2]. The advertising leaflets and producer's notes concerning the medicines containing siloxanes maintain that siloxanes are not absorbed. However, a study by Calandra *et. al.* [3, 4] and our initial work [5] have shown both linear and cyclic siloxanes to become absorbed from the alimentary tract of animals. Only a few toxicological studies have been carried out on the effects of oral or

1) Department of Physical Chemistry, Medical University of Gdańsk.
2) Department of Toxicology, Faculty of Pharmaceutical Sciences, Medical University of Gdańsk.
3) Laboratory of Pathology, Institute of Obstetrics and Women Diseases, Medical University of Gdańsk.
4) Faculty of Biotechnology, University and Medical University of Gdańsk.
5) Faculty of Chemistry, University of Gdańsk, Gdańsk, Poland
*) Address for correspondence: Jerzy Łukasiak, Department of Physical Chemistry, Faculty of Pharmaceutical Sciences, Medical University of Gdańsk, Al. Gen. J. Hallera 107, 80-416 Gdańsk, Poland. Tel. (+48) 58 3493151; e-mail: bogdanf@chemik.chem.univ.gda.pl

parenteral application of liquid siloxanes; some of these results are disquieting [6].

This work is intended to study the absorption of siloxanes from the alimentary tract of rats and their distribution in rat's specific internal organs.

Material and Methods

Animals. Male „Wistar" rats, body weight *ca.* 200 g, were used. The daily intake of feed by each rat was *ca.* 50 g.

Diet containing silicones and control diet. Each control group was fed on a granulated LSM fodder produced by the „Wytwórnia Pasz in Motycz", Motycz, Poland; one tested group was given a specially prepared fodder consisting of 95% LSM and 5% OM-300 — polydimethylsiloxane oil, viscosity about 300 cSt (most frequently given in oral medicines); another group was fed on a specially prepared fodder consisting of 95% LSM and 5% polydimethylcyclosiloxane oil (cPDMS) which was a 1:1 mixture of hexamethyltricyclosiloxane (D_3) and octamethyltetracyclosiloxane (D_4).

Absorption and distribution of orally given siloxanes. Nine rats were studied over a 24-hour period. The control group consisted of 3 rats; the two other groups — each comprising 3 animals — were given a feed containing siloxanes. After being given the first lot of food, one animal from each group was killed in 1 hour, another in 5 hours, and still another in 24 hours. All the blood available, the brain, kidneys, liver and spleen were tested. Silicones were extracted from the tissues, and then determined quantitatively as described below.

Accumulation and toxic effects of orally fed siloxanes on specific internal organs. Fifteen rats were tested for 12 days. The control group consisted of 5 rats; the two other groups — each comprising 5 animals — were given the feed containing PDMS or cPDMS. After 12 days, the animals were killed and all the blood available, the brain, kidneys, liver and spleen were analyzed for siloxanes. The silicones extracted from the blood and organs were quantitatively determined as follows. The internal organs taken for histological examination were: the brain, kidneys, liver, spleen, cardiac muscle, wall of the small intestine, suprarenal gland, pancreas, and lung. Samples were fixed in 10% buffered formalin, treated by the paraffin method, and the dyed with haematoxylin and eosin; the McManus PaS reaction was carried out, too.

Examination of orally administered siloxane in the 24-hour urine and feces of rats. Two rats were taken. Together with the LSM diet, one rat was given 1 g of the OM-300 polydimethylsiloxane oil and the other — 1 g of cPDMS oil. The daily quantities of feces and urine were collected and the siloxanes were determined.

Determinations of siloxanes in blood and organs. Silicones were extracted with CCl_4 from the blood and from the preliminarily homogenized tissues and then determined by recording ^1H NMR spectra (on a Tesla Brno BS-587A type NMR 80 MHz spectrometer) with TSM as an internal standard [7]. The detectability of the method adopted was 10 μg, the determinability was 30 μg; in calculations the samples containing 10—30 μg of siloxanes were treated as containing 10 μg.

Results

Absorption and distribution of orally given siloxanes. Blood was taken, 5—7 mL, from each rat. No signs attributable to the siloxanes were observed in any sample withdrawn from the control groups of animals. Siloxanes were detected in the blood or in particular internal organs (brain, kidneys and liver) of rats as quickly as 1 hour after the rats received the first oral dose of siloxanes (not shown). Table 1 lists the contents of the siloxanes in the blood and in the chosen internal organs of rats 12 days after they had been fed with or without the addition of the siloxanes. A mean concentration of 26±14 μg/mL was found in the blood sample withdrawn from the animals fed for 12 days on the fodder containing cPDMS similar samples withdrawn from the animals fed on the fodder containing cPDMS revealed the value of 70±97 μg/mL. The differences in the contents of siloxanes in the blood and in the organs of comparative groups of rats studied were statistically insignificant, with the exception of the siloxane content in the brain tissue, which was higher in the group of animals fed with PDMS (U Mann-Whitney test, $p = 0.009$).

Table 1. **Mean siloxane contents in the blood and in selected internal organs of rats to which siloxanes were orally administered for 12 days**

Silicones in the diet of rats studied	No. of animals (total = 15)	Silicone contents (mean±SD, μg)				
		blood	brain	kidneys	liver	spleen
None	5	0	0	0	0	0
PDMS	5	150±91	18±18	26±21	0	2±4
cPDMS	5	365±482	0	6±5	0	2±4

The quantity of siloxanes in the daily output of urine and feces after oral dosage. The diurnal urine and the feces of the animal that has received linear siloxanes were found to contain 300 μg and 800 mg silicones, respectively. For the animal that has received cyclic siloxanes the quantities were 10—30 μg of silicones in urine and 400 mg in feces.

Histological assessment of toxic effects in specific organs following oral dosage of siloxanes. No differences attributable to the toxic effects of siloxanes were established between the histological features of the groups of animals studied.

Discussion

The present results concerning the absorption of oral doses of siloxanes clearly indicate comparable absorption of linear and cyclic siloxanes from the alimentary tract of rats. Differences are seen to occur in the tendencies to absorb particular forms of siloxanes by particular individuals. Siloxanes were absorbed relatively quickly and were found to occur in various organs 1 hour after oral dosage, the greatest concentration being in the kidneys, where they are likely to be metabolized and to a slight extent excreted in urine. The siloxanes absorbed are distributed in various organs: in our studies PDMS were preferentially absorbed by the brain tissue and the kidneys, whereas cPDMS remained mainly in the circulatory system, and some accumulated in the kidneys. Our results differ from those previously published, which indicated the almost sole absorption of low-molecular-weight silicones; in the studies by Calandra *et. al.* [3, 4] and in our preliminary studies [5] cyclic siloxanes were found to undergo a greater absorption, but the difference is statistically insignificant. We are not aware of any other studies concerning the absorption, toxicity, and organ distribution of orally administered siloxanes. Our results prove that the remedies based on PDMS or cPDMS as an active substance, should not be treated as passing unabsorbed through the alimentary tract. In view of the toxicological aspects of food and oral application of medicines containing siloxanes, further studies are required [2, 6. 8].

ACKNOWLEDGMENT

The work was supported by the KBN 4PO5D06612 Research Grant.

REFERENCES

1. Łukasiak J., Falkiewicz B., Dąbrowska E., Stołyhwo M.: *Bromat. Chem. Toksykol.* 1996, **29**, 199.
2. Łukasiak J., Falkiewicz B.: *Food Addit. Contam.* 2000, **17**, 945.
3. Calandra J. C., Keplinger M. L., Hobbs E. J., Tyler L. J.: *Polymer Preprints* 1976, **17**, 12.
4. Final report on the safety of Cyclomethicone. *J. Am. Coll. Toxicol.* 1991, **10**, 9.
5. Łukasiak J., Jamrógiewicz Z., Falkiewicz B.: *Environ. Health Persp.* 1999, **107**, A442.
6. Liebierman M. W., Lykissa E. D., Barrios R., Ou C. N., Kala G., Kala S. V.: *Environ. Health Persp.* 1999, **107**, 161.
7. Jamrógiewicz Z., Łukasiak J., Mojsiewicz K.: *Chem. Anal.* (Warsaw) 1997, **42**, 659.
8. Łukasiak J., Jamrógiewicz Z., Czarnowski W., Krechniak J., Falkiewicz B.: *Bromat. Chem. Toksykol.* 1999, **32**, 99.

Received 14 XII 2000.
Revised version 23 IV 2001.

KALENDARZ IMPREZ

c.d. ze str. 533

4—8 listopada 2002 r. Taipei, Tajwan. **„Polymer Processing Society — Asia/Australia Meeting PPS-2002".**

Organizatorzy: Chang Gung University + The Polymer Processing Society, Taipei.

Tematyka ogólna: formowanie wtryskowe, wytłaczanie, reologia mieszaniny i stopy polimerowe, prace związane z rozwojem zagadnień morfologii i struktury polimerów, kształtowanie termiczne, formowanie z rozdmuchiwaniem, formowanie obrotowe, modelowanie matematyczne, przetwarzanie reaktywne, kompozyty polimerowe, włókna i folie, sporządzanie mieszanek gumowych i mieszanin polimerowych, właściwości mechaniczne, optyczne i elektryczne.

Tematyka specjalistyczna: przetwarzanie żywności, uwidocznianie przepływu, czujniki w procesie przetwarzania, formowanie wtryskowe wspomagane gazem, biopolimery, zastosowania w optyce i elektronice/elektrotechnice, nowe procesy przetwórcze.

Informacje: Dr Shih-Jung Liu, PPS Meeting 2002, Polymer Rheology and Processing Lab, Mechanical Eng., tel.: 886-3-3288 566, fax: 886-3-3972 558, e-mail: shihjung@mail.cgu.edu.tw lub pps2002@mail.cgu.edu.tw, internet: http://pps.cgu.edu.tw.