MMSL Military Medical Science Letters

Mil. Med. Sci. Lett. (Voj. Zdrav. Listy) 2012, vol. 81(2), p. 61-67
ISSN 0372-7025
DOI: 10.31482/mmsl.2012.008

REVIEW ARTICLE

GYROMITRIN, MUSHROOM TOXIN OF *GYROMITRA* SPP.

Jiri Patocka[1]✉, Rene Pita[2] and Kamil Kuca[3,4]

[1] Department of Radiology and Toxicology, Faculty of Health and Social Studies, University of South Bohemia Ceske Budejovice, Ceske Budejovice, Czech Republic
[2] NBC Defence School, Ministry of Defence, Madrid, Spain
[3] Center of Advanced Studies, Faculty of Military Health Sciences, University of Defence, Hradec Kralove, Czech Republic
[4] University Hospital, Hradec Kralove, Czech Republic

Received 3rd May 2012.
Revised 15th May 2012.
Published 8th June 2012.

Summary

Gyromitra esculenta (Persoon ex Fries) mushrooms have been responsible for severe intoxications and even deaths. Clinical data are characterized primarily by vomiting and diarrhea and after a while by jaundice, convulsions and coma. Other *Gyromitra* species which may be of concern are *G. fastigiata* and *G. gigas*; nevertheless, recent advances in chromatography, biochemistry and toxicology have established that other species within the *Ascomycetes* may also prove toxic. Their toxins, mainly gyromitrin (N-methyl-N-formyl-N-acetyl-hydrazone) and their higher homologues are converted in the milieu of human stomach into N-methyl-N-formylhydrazine (MFH), then into N-methylhydrazine (MH). The toxicity of these latter chemicals, which are mainly hepatotoxic and even carcinogenic, has been established through *in vivo* and *in vitro* experiments with cell cultures and biochemical systems. Considering the chemical structure and the reactivity of these natural compounds, chemical and biochemical mechanisms are defined in order to explain their intrinsic biological activity. These findings imply that consumption of *G. esculenta* could present a carcinogenic as well as an acutely toxic health hazard.

Key words: Gyromitra esculenta; mycotoxin; gyromitrin; N-methyl-N-formyl-N-acetyl-hydrazone; N-methyl-N-formyl-hydrazine

INTRODUCTION

Gyromitra is a genus of ascomycete mushrooms (*Ascomycota* phylum) found in the northern hemisphere. The genus *Gyromitra* contains about 18 species (Stephenson, 2010). Some types of *Gyromitra* are highly poisonous when raw, and these mushrooms have caused severe poisonings and even deaths in humans (Michelot and Toth, 1991). Clinical data are characterized primarily by vomiting and diarrhea, followed by jaundice, convulsions and coma (Hendricks, 1940). Gastrointestinal disorders distinguish this poisoning. Frequent consumption can cause hepatitis and neurological diseases (Köppel, 1993). The species of concern are mainly *G. esculenta*, as well as *G. gigas* (Kromb.). Nevertheless, recent advances in chromatography, biochemistry and toxicology have established that other *Gyromitra* species may also prove toxicity (Patowary, 2010), although some are edible when cooked.

✉ University of South Bohemia České Budějovice, Faculty of Health and Social Studies, Department of Radiology and Toxicology, Matice školské 17, 370 01 České Budějovice, Czech Republic
prof.patocka@gmail.com

G. esculenta is very sought after in Scandinavian countries (Härkönen, 1998), while its sale or trading is illegal in some European countries (Ludolph, 2000). Consumption of false morel has been associated not only with acute poisoning, but also with a carcinogenic risk (Bergman and Hellenäs, 1992).

Chemistry of toxic principles

Gyromitrin (ethylidene gyromitrin, acetaldehyde N-methyl-N-formylhydrazone) and its homologues are toxic compounds present in raw edible wild mushroom *G. esculenta*. They are converted *in vivo* into *N*-methyl-N-formylhydrazine (MFH), and then into *N*-methylhydrazine (MH) (Fig. 1), which is highly toxic (Nagel et al., 1977; List and Luft, 1968). In studies on volatile compounds in false morels it has been found that in addition to gyromitrin these mushrooms contain also other toxic hydrazones. They were identified as higher homologues of gyromitrin, i.e. N-methyl N-formyl hydrazones of pentanal, 3-methylbutanal, and hexanal (Fig. 2) (Pyysalo, 1975). The toxicity of these chemicals, which are mainly hepatotoxic and even carcinogenic, has been established through *in vivo* and *in vitro* experiments using animals, cell cultures and biochemical systems. Presumably all these compounds yield MH on hydrolysis, which is probably the highly toxic compound formed after false morels ingestion (Wright et al., 1978). The presence of these hydrazine derivatives has recently been confirmed at levels of 0.3% gyromitrin and 0.05% MFH in dried mushrooms (Schmidlin-Mészáros, 1974).

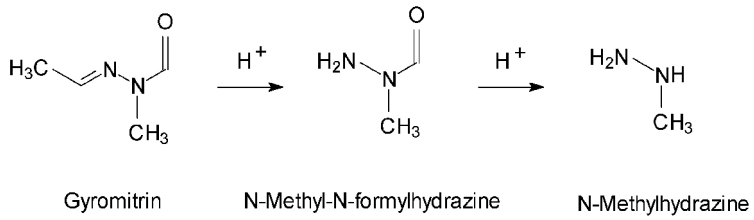

Figure 1. Gyromitrin (acetaldehyde N-methyl-N-formylhydrazone) is converted *in vivo* into *N*-methyl-N-formylhydrazine, and then into *N*-methylhydrazine.

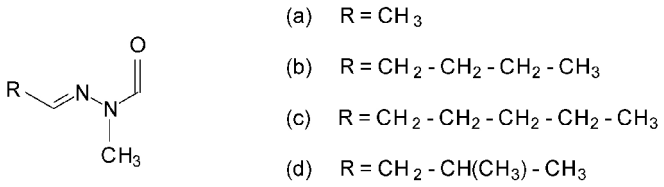

Figure 2. Structures of toxic compounds in fresh false morel (*Gyromitra esculenta*). (a) Acetaldehyde N-methyl-N-formyl hydrazone (gyromitrin), (b) pentanal N-methyl-N-formyl hydrazone, (c) hexanal N-methyl-N-formyl hydrazone, (d) 3-methylbutanal N-methyl-N-formyl hydrazone.

Poisoning by Gyromitra

Gyromitra species are considered to be edible mushrooms although their potential toxicity has been long known. They have caused numerous accidents, sometimes lethal (Giusti and Carnevale, 1974; Michelot, 1989). Historical accounts of poisoning are reported and the authors describe the main characteristics: inconstant toxicity, influence of repetitive ingestions and variable individual sensitivity. Knowing that gyromitrin can be converted into MH, the authors suggest a relation between individual sensitivity to the mushrooms and variation of interhuman ability to carry out such a conversion. Several metabolites of gyromitrin can produce enzyme activation with subsequent synthesis

of MH. The cumulative activating role of consecutive ingestions is emphasized (Coulet and Guillot, 1982).

Acute poisoning by *Gyromitra* is scarce in Western Europe while it is the most frequent in Eastern Europe (Raszeja, 1959; Fiedorowicz-Fabrycy and Lapis, 1968; Eisner et al., 1973; Giusti and Carnevale, 1974; Garnier et al., 1978; Flammer, 1985; Kohn and Mot'ovská, 1997). Poisonings cases have been described in the American continent as well (Leathem and Dorran, 2007). A *G. esculenta* fatal hemolytic episode in a dog has also been described (Bernard, 1979).

Giusti and Carnevale (1974) reported a case of fatal poisoning by *G. esculenta* in a 53-year-old woman. Clinical data were characterized initially by vomiting and diarrhea, and subsequently by hypotension, anuria, jaundice, hemiplegia, and coma. Death followed on the third day. Prominent pathologic findings were brain edema, necrosis, fatty degeneration of the liver, nephrosis, scattered petechiae, and small hemorrhages.

Gyromitra poisoning clinical picture associating cytolytic hepatitis, seizures, and hemolysis reminds us of hydrazine poisonings (Mittmann, 1968; Garnier et al., 1978). Primary hemolysis induced by antigens and toxins of mushrooms must be distinguished from secondary hemolysis of shock and disseminated intravascular coagulation with disruption of erythrocytes (Flammer and Gallen, 1983). In the most severe cases, death occurs 3 or 5 days after ingestion. Hydrazine derivatives are also known to bind vitamin B_6, thus this could be the mechanism of action for some neurotoxic effects observed in *Gyromitra* poisonings (Ludolph, 2000). In fact, administration of vitamin B_6 is suggested to prevent seizures (Michelot and Toth, 1991).

Toxic compounds

Gyromitrin is the main poisonous hydrazine derivative present in *G. esculenta*, but its metabolites MFH and MH are also very important toxic products (Coulet and Guillot, 1982).

Gyromitrin

Gyromitrin (CAS Registry Number 16568-02-8) LD_{50} acute oral toxicity is: 344 mg/kg in mice (Wright et al., 1978), 320 mg/kg in rats (Mäkinen et al., 1977), while in rabbits it varies from 50 mg/kg (Pyysalo, 1975) to 70 mg/kg (Mäkinen et al., 1977). No toxic effects were detected in chickens when given a dose of 400 mg/kg (Mäkinen et al., 1977). Gyromitrin had no detectable toxic effect on the bacterium *Escherichia coli* (Wright et al., 1977). The gyromitrin content of dried false mushrooms has been found to be between 0.05 and 0.3 percent. It is estimated that 99.9 % of the gyromitrin in a mushroom is lost by boiling and up to 99 % is lost by drying.

In rats gyromitrin caused an increased diuresis in which urine was produced with a weak alkaline pH, as well as a high excretion of sodium (530 %) and potassium (210 %). The observed increase lasted for about 12 h and was followed by a retention with regard to the volume and the sodium excretion for about 72 h. On the basis of [3H] inulin excretion, an increased glomerular filtration was observed followed by a decrease 12 h after application of gyromitrin (Braun et al., 1979).

Clonic-tonic convulsions, hypersensitivity, loss of activity, lack of appetite and severe weight loss were observed in rabbits and rats after administration of gyromitrin. Haemoglobinuria, proteinuria, bilirubinuria and a decrease in urinary pH were evident in affected rabbits and concentrations of creatine, bilirubin and activities of aspartate and alanine aminotransferases were abnormally high in the serum. Rabbits that died showed extensive fatty degeneration of the liver, but this effect was much less severe in rats (Mäkinen et al., 1977).

Gyromitrin was not shown to be mutagenic in bacteria (Wright et al., 1977), but some authors conclude that gyromitrin is carcinogenic in experimental animals (Braun et al. 1981). No data is available to establish carcinogenicity in humans. Although there are no case reports or epidemiological studies available to evaluate carcinogenicity in humans, it is reasonable to regard the compound as if it presented a carcinogenic risk (Anonymous, 1983).

N-Methyl-N-formyl hydrazine

N-methyl-N-formyl hydrazine (MFH) (CAS Regisry Number 758-17-8) is formed from gyromitrin by hydrolytic cleavage *in vivo* and *in vitro* during food processing (Nagel et al., 1977), but it is also a stable constituent of the edible false morel mushroom *G. esculenta* (Toth and Patil, 1982). MFH

is hepatotoxic and carcinogenic (Braun et al., 1979, 1981; Toth and Patil, 1979). Its mode of action, however, is poorly understood. Gannet et al. (1991) found that microsome-mediated oxidation of MFH yielded formaldehyde and acetaldehyde. The formation of acetaldehyde requires (i) the oxidation of MFH to a diazenium ion or diazene and (ii) fragmentation of these ions to formyl and methyl radicals. It is suggested that these radical intermediates may be important in understanding and elucidating carcinogenesis by MFH (Gannett et al., 1991).

Continuous administration of 0.0078% MFH in drinking water to 6-week-old outbreed Swiss mice for life produced tumors of the liver, lung, gallbladder, and bile duct (Toth and Nagel, 1978; Toth et al., 1979). Histopathologically, the tumors were classified as benign hepatomas, liver cell carcinomas, angiomas and angiosarcomas of blood vessels, and adenomas and adenocarcinomas of lungs. From representative samples of these neoplasms detailed transmission electron microscopic investigations were also carried out. Since these hydrazine analogs induce tumors in animals and these mushrooms are consumed on a large scale by humans in various parts of the world, their hazardous nature should be considered (Toth, 1979; Toth and Patil, 1980a,b).

LD_{50} acute oral toxicity of MFH in mouse is 118 mg/kg (Wright et al., 1978) and in rat 400 mg/kg (Kreybig et al., 1970). MFH is an inhibitor of human intestinal diamine oxidase (Biegański et al., 1980), but this effect is not probably important for the toxic effect of MFH.

N-Methylhydrazine

N-Methylhydrazine (MH) (CAS Registry Number 60-34-4) is a metabolite of gyromitrin, but is also a stable component of *G. esculenta*. MH has many industrial and commercial uses. For example, it has military applications as a rocket propellant in bipropellant rocket engines. Table 1 summarizes acute toxicity parameters (LC_{50} and LD_{50} values) for MH in different laboratory animals experiments.

Table 1. Toxic parameters of N-methylhydrazine acute toxicity.

Organism	Test type	Route	Reported Dose	Source
Dog	LC_{50}	inhalation	96 ppm/1 hour	Haun et al., 1970
Dog	LD_{50}	intravenous	12 mg/kg	Smith et al., 1969
guinea pig	LD_{50}	skin	48 mg/kg	Smith et al., 1969
Hamster	LD_{50}	intraperitoneal	21 mg/kg	Gregory et al., 1971
Hamster	LD_{50}	oral	22 mg/kg	Gregory et al., 1971
Hamster	LD_{50}	skin	239 mg/kg	Gregory et al., 1971
Monkey	LC_{50}	inhalation	82 ppm/1 hour	Haun et al., 1970
Mouse	LD_{50}	intraperitoneal	15 mg/kg	Furst et al., 1967
Mouse	LD_{50}	subcutaneous	25 mg/kg	Hawks et a., 1974
Rabbit	LD_{50}	intravenous	12 mg/kg	Smith et al., 1969
Rabbit	LD_{50}	skin	95 mg/kg	Smith et al., 1969
Rat	LD_{50}	intraperitoneal	21 mg/kg	Gregory et al., 1971
Rat	LD_{50}	intravenous	17 mg/kg	Gregory et al., 1971
Rat	LD_{50}	skin	183 mg/kg	Gregory et al., 1971
Rat	LD_{50}	subcutaneous	35 mg/kg	Hawks et al, 1974

Acute inhalation exposure to high levels of MH may cause lacrimation, eye redness, nasal and respiratory irritation, headache, malaise, vomiting, diarrhea, ataxia, anoxia, cyanosis, tremors, and convulsions in humans (George et al., 1982). Acute exposure to MH in humans has also been observed to affect the blood, kidneys, and liver (Mori et al., 1988). MH is highly corrosive and irritating to

the skin, eyes, and mucous membranes of the respiratory system in humans and animals (Haun et al., 1970).

Chronic inhalation exposure to MH has been observed to impair function of the kidneys and liver, affect the blood and spleen, and cause convulsions in animals. MH significantly increased the incidence of lung tumors in Swiss mice (Toth, 1972). Nevertheless, the US Environmental Protection Agency has not classified MH for carcinogenicity (Reddy et al., 2010) and teratogenicity (Keller et al., 1984; Slanina et al., 1993).

CONCLUSIONS

Consumption of false morel has been associated not only with acute poisoning, but also with a carcinogenic risk. Gyromitrin, acetaldehyde *N*-methyl-*N*-formylhydrazone, and N-methylhydrazine are toxins present in edible wild mushroom *G. esculenta*. N-methylhydrazine is a tumor inducer in mice and hamsters, through an intermediate, *N*-methyl-*N*-formylhydrazine. In addition, methylhydrazine is formed in a mouse stomach after p.o. administration of gyromitrin. These findings imply that consumption of *G. esculenta* could present a carcinogenic as well as an acutely toxic health hazard.

ACKNOWLEDGMENTS

This work was supported by the projects MO0FVZ0000604 and MZO 00179906.

REFERENCES

1. Anonymous. IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans Vol: 31, **1983**, 163-170.
2. Bergman, K.; Hellenäs, K.E. Methylation of rat and mouse DNA by the mushroom poison gyromitrin and its metabolite monomethylhydrazine. *Cancer Lett.*, **1992**, 61(2), 165-170.
3. Bernard, M.A. Mushroom poisoning in a dog. *Can Vet J.*, **1979**, 20(3), 82-83.
4. Biegański, T.; Kusche, J.; Feussner, K.D.; Hesterberg, R.; Richter, H.; Lorenz, W. The importance of human intestinal diamine oxidase in the oxidation of histamine and/or putrescine. *Arch Immunol Ther Exp (Warsz)*, **1980**, 28(6), 901-906.
5. Braun, R.; Dittmar, W.; Greeff, U. Considerations on the carcinogenicity of the mushroom poison gyromitrin and its metabolites. *J Appl Toxicol*, **1981**, 1(5): 243-246.
6. Braun, R.; Greeff, U.; Netter, K.J. Liver injury by the false morel poison gyromitrin. *Toxicology*, **1979**, 12(2), 155-163.
7. Braun, R.; Kremer, J.; Rau, H. Renal functional response to the mushroom poison gyromitrin. *Toxicology*, **1979**, 13(2), 187-196.
8. Braun, R.; Weyl, G.; Netter, K.J. The toxicology of 1-acetyl-2-methyl-2-formyl hydrazine (Ac-MFH). *Toxicol Lett*., **1981**, 9(3), 271-277.
9. Coulet, M.; Guillot. J. Poisoning by *Gyromitra*: a possible mechanism. *Med Hypotheses*, **1982**, 8(4), 325-334.
10. Eisner, M.; Kurovski, M.; Pilarska, K.; Koszarska, J.; Goertz, J. *Gyromitra esculenta* poisoning. *[Article in Polish] Pol Tyg Lek*., **1973**, 28(49), 1536-1539.
11. Fiedorowitz-Fabrycy, I.; Lapis, J. Poisoning with *Gyromitra esculenta. [Article in Polish] Wiad Lek*., **1968**, 21(6), 489-491.
12. Flammer, R.; Gallen, S. Hemolysis in mushroom poisoning: facts and hypotheses. *[Article in German] Schweiz Med Wochenschr*, **1983**, 113(42), 1555-1561.
13. Flammer, R. Gyromitra syndrome: poisoning by the spring false morel. *[Article in German]. Schweiz Rundsch Med Prax*., **1985**, 74(37), 983-984.
14. Furst, A.; Gustavson, W.R. A comparison of alkylhydrazines and their B 6-hydrazones as convulsant agents. *Proc Soc Exp Biol Med*., **1967**, 124(1),172-175.
15. Gannett, P.M.; Garrett, C.; Lawson, T.; Toth, B. Chemical oxidation and metabolism of N-methyl-N-formylhydrazine. Evidence for diazenium and radical intermediates. *Food Chem Toxicol*, **1991**, 29(1), 49-56.
16. Garnier, R.; Conso, F.; Efthymiou, M.L.; Riboulet, G.; Gaultier, M. Acute poisoning by *Gyromitra esculenta. [Article in French] Toxicol Eur Res*., **1978**, 1(6), 359-364.
17. George, M.E.; Pinkerton, M.K.; Back, K.C. Therapeutics of monomethylhydrazine intoxication. *Toxicol Appl Pharmacol*, **1982**, 63(2), 201-208.
18. Giusti, G.V.; Carnevale, A. A case of fatal poisoning by *Gyromitra esculenta. Arch Toxicol*, **1974**, 33(1), 49-54.

19. Gregory, A.R.; Legg, C.A.; Cornish, M.H.; Evans, D.Q. Space propellant residues. *Clin Toxicol*, **1971**, 4(3), 435-450.
20. Haun, C.C.; Macewen, J.D.; Vernot, E.H.; Eagan, G.F. Acute inhalation toxicity of monomethylhydrazine vapor. *Am Ind Hyg Assoc J*., **1970**, 31(6),667-677.
21. Hawks, A.; Hicks, R.M.; Holsman, J.W.; Magee, P.N. Morphological and biochemical effects of 1,2-dimethylhydrazine and 1-methylhydrazine in rats and mice. *Br J Cancer*, **1974**, 30(5), 429-439.
22. Härkönen, M. Uses of mushrooms by Finns and Karelians. *Int J Circumpolar Health*, **1998**, 57(1), 40-55.
23. Hendricks, H.V. Poisoning by false morel (*Gyromitra esculenta*). *JAMA*, **1940**, 114(17), 1625.
24. Keller, W.C.; Olson, C.T.; Back, K.C.; Gaworski, C.L. Teratogenic assessment of three methylated hydrazine derivatives in the rat. *J Toxicol Environ Health*, **1984**, 13(1), 125-131.
25. Kohn, R.; Moťovska, Z. Mushroom poisoning--classification, symptoms and therapy. *[Article in Slovak] Vnitr Lek.*, **1997**, 43(4), 230-233.
26. Kreybig, von T.; Preussmann, R.; Kreybig, von I. Chemical constitution and teratogenic effect in rats. 3. N-alkylcarbonhydrazides, hydrazine derivatives. *[Article in German] Arzneimittelforschung*, **1970**, 20(3), 363-367.
27. Leathem, A.M.; Dorran, T.J. Poisoning due to raw *Gyromitra esculenta* (false morels) west of the Rockies. *CJEM*, *2007*, 9(2), 127-130.
28. Ludolph, A.C. Gyromitrin. In: Spencer, P.S.; Scheumburg, H.H.; Ludolph, A.C. (eds.), Experimental and Clinical Neurotoxicology. *Oxford University Press*, **2000**, 619-620. ISBN 0-19-508477-2.
29. Mäkinen, S.M.; Kreula, M.; Kauppi, M. Acute oral toxicity of ethylidene gyromitrin in rabbits, rats and chickens. *Food Cosmet Toxicol*, **1977**, 15(6), 575-578.
30. Michelot, D. Poisoning by Geromitra esculenta. *[Article in French] J Toxicol Clin Exp*., **1989**, 9(2), 83-99.
31. Michelot, D.; Toth, B. Poisoning by Gyromitra esculenta – a review. **1991**, *J Appl Toxicol*, 11(4), 235-243.
32. Mittmann, W. On the clinical picture and therapy of edible gyromitra poisoning (*Gyromitra esculenta*). *[Article in German] Z Arztl Fortbild (Jena)*, **1968**, 62(13), 710-713.
33. Mori, H.; Sugie, S.; Yoshimi, N.; Iwata, H.; Nishikawa, A.; Matsukubo, K.; Shimizu, H.; Hitono, I. Genotoxicity of a variety of hydrazine derivatives in the hepatocyte primary culture/DNA repair test using rat and mouse hepatocytes. *Jpn J Cancer Res*., **1988**, 79(2), 204-211.
34. Nagel, D.; Wallcave, L.; Toth, B.; Kupper, R. Formation of methylhydrazine from acetaldehyde N-methyl-N-formylhydrazone, a component of *Gyromitra esculenta. Cancer Res*., **1977**, 37(9), 3458-3460.
35. Köppel, C. Clinical symptomatology and management of mushroom poisoning. *Toxicon*, **1993**, 31(12), 1513-1540.
36. List, P.H.; Luft P. Gyromitrin, the poison of *Gyromitra esculenta*. 16. On the fungi contents. *[Article in German] Arch Pharm Ber Dtsch Pharm Ges*., **1968**, 301(4), 294-305.
37. Ludolph, A.C. Gyromitrin. In: Spencer, P.S.; Scheumburg, H.H.; Ludolph, A.C. (eds.), Experimental and Clinical Neurotoxicology. *Oxford University Press*, **2000**, 619-620. ISBN 0-19-508477-2.
38. Patowary, B.S. Mushroom poisoning – an overview. *J Coll Med Sci Nepal*, **2010**, 6(2), 56-61.
39. Patočka, J. Gyromitrin – main toxic effect. Server TOXICOLOGY. Available online: http://toxicology.cz/modules.php?name=News&file=article&sid=238
40. Pyysalo, H. Some new toxic compounds in false morels, *Gyromitra esculenta. Naturwissenschaften*, **1975**, 62, 395.
41. Raszeja S. Diagnosis of fatal *Gyromitra esculenta poisoning. [Article in Polish] Patol Pol*., **1959**, 10(1), 35-60.
42. Reddy, G.; Song, J.; Mecchi, M.S.; Johnson, M.S. Genotoxicity assessment of two hypergolic energetic propellant compounds. *Mutat Res*., **2010**, 700(1-2), 26-31.
43. Schmidlin-Mészáros, J. Gyromitrin in Trockenlorcheln (*Gyromitra esculenta* sice.). *Mitt. Gebiete Lebensm. Hyg*., **1974**, 65, 453-465.
44. Slanina, P.; Cekan, E.; Halen, B.; Bergman, K.; Samuelsson, R. Toxicological studies of the false morel (*Gyromitra esculenta*): embryotoxicity of monomethylhydrazine in the rat. *Food Addit Contam*, **1993**, 10(4), 391-398.
45. Smith, E.B.; Clark, D.A. The absorption of monomethylhydrazine through canine skin. *Proc Soc Exp Biol Med*., **1969**, 131(1), 226-232.
46. Stephenson, S.L. The Biology of Mushrooms, Molds, and Lichens. *Timber Press*, **2010**, 272 pages. ISBN 978-0-88192-891-4
47. Toth, B. Hepatocarcinogenesis by hydrazine mycotoxins of edible mushrooms. *J Toxicol Environ Health*, **1979**, 5(2-3), 193-202.

48. Toth, B. Hydrazine, methylhydrazine and methylhydrazine sulfate carcinogenesis in Swiss mice. Failure of ammonium hydroxide to interfere in the development of tumors. *Int J Cancer*, **1972**, 9(1), 109-118.
49. Toth, B.; Nagel, D. Tumors induced in mice by N-methyl-N-formylhydrazine of the false morel *Gyromitra esculenta. J Natl Cancer Inst*., **1978**, 60(1), 201-204.
50. Toth, B.; Patil K. Carcinogenic effects in the Syrian golden hamster of N-methyl-N-formylhydrazine of the false morel mushroom *Gyromitra esculenta. J Cancer Res Clin Oncol*, **1979**, 93(2), 109-121.
51. Toth, B.; Patil K.; Erickson, J.; Kupper, R. False morel mushroom *Gyromitra esculenta* toxin: N-methyl-N-formylhdrazine carcinogenesis in mice. *Mycopathologia*, **1979**, 68(2), 121-128.
52. Toth, B.; Patil K. Carcinogenesis by a single dose of N-methyl-N-formylhydrazine. *J Toxicol Environ Health*, **1980a**, 6(3), 577-584.
53. Toth, B.; Patil K. The tumorigenic effect of low dose levels of N-methyl-N-formylhydrazine in mice. *Neoplasma*, **1980b**, 27(1), 25-31.
54. Toth, B.; Patil K. Tumorigenic action of repeated subcutaneous administration of N-methyl-N-formylhydrazine in mice. *Neoplasma*, **1983**, 30(4), 437-441.
55. Toth, B.; Patil K. Tumorigenicity of minute dose levels of N-methyl-N-formylhydrazine of *Gyromitra esculenta. Mycopathologia*, **1982**, 78(1), 11-16.
56. Wright, von A.; Niskanen, A.; Pyysalo, H.; Korpela, H. The toxicity of some N-methyl-N-formylhydrazones from *Gyromitra esculenta* and related compounds in mouse and microbial tests. *Toxicol Appl Pharmacol*, **1978**, 45(2), 429-434.
57. Wright, von A.; Niskanen, A.; Pyysalo, H. Mutagenic properties of ethylidene gyromitrin and its metabolites in microsomal activation tests and in the host-mediated assay. *Mutat Res*., **1978**, 54(2), 167-173.
58. Wright, von A.; Niskanen, A.; Pyysalo, H. The toxicities and mutagenic properties of ethylidene gyromitrin and N-methylhydrazine with Escherichia coli as test organism. *Mut Res Fundam Mol Mechan Mutagen*, **1977**, 56(2), 105-110.