FFI JOURNAL, Vol. 225, No.2, 2020

The Pathology of Selected Dietary Herbal Medicines as Observed in the National Toxicology Program Studies

Abraham Nyska[a)] Shim-mo Hayashi[b)]
Robert R. Maronpot[c)] Yuval Ramot[d)]
[a)] Consultant in Toxicologic Pathology, Timrat and Tel Aviv University Haharuv 18, P.O. Box 184, Timrat 36576, Israel.
[b)] Division of Food Additives, National Institute of Health Sciences, Kawasaki, Japan
[c)] Maronpot Consulting LLC, Raleigh, North Carolina, USA
[d)] Hadassah Medical Center, Hebrew University of Jerusalem, The Faculty of Medicine, Jerusalem, Israel

Summary

The popularity of herbal medicines is growing steadily all over the world, and a large number of people are using these products for self-medication. Although these medicines are being widely used, and the number of available products is increasing exponentially, most of these compounds have not been properly evaluated for potential toxic or adverse effects. It is on this background that the National Toxicology Program has performed comprehensive 2-year rodent studies to evaluate the toxicity and safety of popular herbal medicines, including Aloe vera, ginkgo, ginseng, goldenseal, kava kava, milk thistle, and turmeric oleoresin. Here we review the pathological findings in rodents, with special emphasis on the carcinogenic potential of these compounds, which included liver tumor responses (goldenseal, ginkgo, kava), intestinal tumor response (aloe vera whole leaf non-decolorized extract) and thyroid tumor response (ginkgo). The results of these studies together with information gathered from additional clinical trials from other NIH institutes would provide a more complete evaluation of the risk and benefits from herbal medicine use.

1. Introduction

The popularity of herbal medicines is growing steadily all over the world, and a large number of people are using these products for self-medication[1)]. The use of herbal medicines is especially popular in developing countries, where 80% of the population use herbal medicines as their main medical treatment[2)], but its use is also growing rapidly in popularity in developed countries. It was estimated that 67.6% of the United States population had used herbal medicines, 52.1% in South Australia and 70% in Germany[3)].

Although these medicines are widely used, and the number of available products is increasing exponentially, most of these compounds have not been properly evaluated for potential toxic or adverse effects. This is especially true for the possible more insidious and chronic effects that might result from chronic exposure to herbal medications. Indeed, in recent years, there is an increasing concern that medications that derive from plants can lead to hormonal changes, disturbance of developmental and reproductive processes, and carcinogenicity[4)], even in very low concentrations. Therefore, it has become apparent that full safety evaluation should be conducted for these compounds, and especially long-term carcinogenicity and reproductive toxicity studies[3)].

It is on this background that the National Toxicology Program (NTP) has performed comprehensive 2-year rodent studies to evaluate the toxicity and safety of

＊This review is based on and adapted from the previously published article by Dunnick JK and Nyska A (2013): "The toxicity and pathology of selected dietary herbal medicines." Toxicol Pathol. 41(2):374-86.

popular herbal medicines, including Aloe vera, ginkgo, ginseng, goldenseal, kava kava, milk thistle, and turmeric oleoresin. The main pathological diagnoses of these studies have been published before[5], but in this review we expand and review in more detail the pathological findings in rodents, with special emphasis on the carcinogenic potential of these compounds.

2. Materials and Methods

The chemical constituents of all the herbal products described in this paper were analyzed using chromatographic techniques as described in the NTP technical report series (https://ntp.niehs.nih.gov/results/summaries/chronicstudies/index.html). The animals that were selected for the NTP 2-year studies included male and female F344/N rats and B6C3F1 mice (5-6 weeks of age at the start of the study), that were administered the tested compounds 5 days per week either by feed or by oral gavage. The animals were kept five female rats or mice per cage, two-to-three male rats per cage, and one male mouse per cage. NTP-2000 diet and tap water were provided *ad libitum*. The animals were treated according to NIH procedures as described in the "The U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals", available from the Office of Laboratory Animal Welfare, National Institutes of Health, Department of Health and Human Services, RKLI, Suite 360, MSC 7982, 6705 Rockledge Drive, Bethesda, MD 20892-7982 or online at http://grants.nih.gov/grants/olaw/olaw.htm#pol. Moribund animals were sacrificed during the study period, and complete necropsies were performed on all animals. For histopathological evaluation, tissues were preserved in 10% neutral buffered formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. All histopathologic diagnoses of neoplasms and findings in target organs were subject to quality assessment by a pathology working group[6,7]. Neoplasm and nonneoplastic lesion prevalence was assessed using the poly-3 test, a test that takes survival differences into account[8-10].

3. Results

3-1. Ginkgo biloba extract – Male and female rats and mice (oral gavage)

(TR-578: https://ntp.niehs.nih.gov/results/summaries/chronicstudies/index.html)

A clear carcinogenic effect was not observed in the rat studies. However, target organ toxicities were seen in the liver, thyroid, and nasal cavity. In the liver, the incidence of bile duct hyperplasia and centrilobular hepatocyte hypertrophy was increased, in addition to increased incidence of fatty changes in females and clear cell focus and oval cell hyperplasia in males. In the thyroid gland, the incidence of thyroid follicular cell hyperplasia and hypertrophy was increased, and there was an increase in the incidence of thyroid gland follicular cell tumors in some treatment-groups, that although not statistically significant, it was outside of the historical control range.

In the nose, transitional and respiratory epithelium hyperplasia and atrophy, respiratory metaplasia, nerve atrophy, and pigmentation in the olfactory epithelium were increased in almost all treatment groups. Additional significant findings included goblet cell hyperplasia in the respiratory epithelium, submucosa fibrosis and chronic active inflammation in the higher doses. Two adenomas of the respiratory epithelium were found in 300 mg/kg females. This is a very rare neoplasm in rats, and therefore this finding might have been related to treatment.

In contrast to the rat studies, where a clear carcinogenic effect was not observed with ginkgo biloba extract administration, a carcinogenic reaction was clearly evident in the liver of males and female mice. The incidence of hepatocellular adenoma or carcinoma, or hepatoblastoma (combined) was significantly increased in all the treatment groups. The hepatocellular adenomas were generally well-circumscribed neoplasms composed of well-differentiated hepatocytes that were variable in size and tinctorial characteristics (i.e., eosinophilic, basophilic, clear, vacuolated, or an admixture). Some carcinomas had a solid growth pattern while a trabecular pattern composed of cords of hepatocytes (three or more cell layers-thick) was also common. Trabeculae were separated by dilated vascular spaces. When the solid growth pattern was

present, the cells tended to be anaplastic, consisting of large cells with large hyperchromatic irregularly shaped nuclei, double nuclei, two or three nucleoli, abundant eosinophilic cytoplasm, or scant basophilic cytoplasm, and numerous areas with two or three mitotic figures per high-power field.

Hepatoblastomas were characterized by an irregular mass of compact basophilic neoplastic cells arranged in sheets with palisading around vascular spaces. Nuclei were generally irregularly oval-to-round with a scant amount of basophilic cytoplasm; mitotic figures were numerous. Blood-filled cystic spaces, necrosis, and hemorrhage were common. The hepatoblastomas frequently arose within hepatocellular carcinomas and hepatocellular adenomas. When the hepatoblastomas arose within or at the margin of either a hepatocellular adenoma or a hepatocellular carcinoma they were recorded as a hepatoblastoma.

In addition to the carcinogenic effects in the liver, additional non-neoplastic lesions were observed in this organ, including liver hypertrophy and hepatocytic erythrophagocytosis.

As in the rats, there was an increase in the incidence of thyroid gland hyperplasia and follicular cell hypertrophy in some of the treatment groups, and two follicular cell adenomas were observed. In the nose, there was an increase in the incidence of pigmentation and hyaline droplet accumulation in the olfactory epithelium in the higher dosed groups.

3-2. Goldenseal – Male and female rats and mice

(TR-562: https://ntp.niehs.nih.gov/results/summaries/chronicstudies/index.html).

There was an increased incidence and earlier time to first appearance of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined) in the high dose animals, which was considered as evidence for carcinogenic activity.

The hepatocellular adenomas were typically composed of solid sheets of large eosinophilic, often vacuolated cells without normal hepatic lobular architecture. There was compression of the surrounding non-neoplastic liver parenchyma. Multiple hepatocellular adenomas were seen in two 25,000 ppm males. The hepatocellular carcinoma in one 25,000 ppm male was a large mass composed of large, pleomorphic, markedly vacuolated cells that formed trabeculae often more than five hepatocytes thick.

Non-neoplastic hepatic lesions that were attributed to treatment included hepatocyte hypertrophy, hepatocyte degeneration, eosinophilic focus, and mixed cell focus.

In mice, the incidence of hepatocellular adenoma was increased. However, although there was an increase in the incidence of hepatocellular carcinoma, it was not statistically different from vehicle-treated animals, in contrast to the findings in rats. The hepatocellular adenomas were discrete masses with distinct borders that caused compression of the surrounding normal hepatic parenchyma, sometimes projecting above the surface of the liver. They were composed of mildly-to-moderately pleomorphic hepatocytes that were of normal size or slightly larger than normal. Microscopically, the hepatoblastomas were usually well demarcated from the surrounding tissue. They consisted of nests, clusters, or sheets of small-to medium-sized, generally spindle-shaped cells that had scant amounts of deeply basophilic cytoplasm and round-to-oval hyperchromatic nuclei. Hepatoblastomas sometimes occurred within a hepatocellular carcinoma and at other times appeared to arise directly from the liver parenchyma. There was also an increase in the number of neoplastic foci in male mice.

3-3. Kava kava extract– Male and female rats and mice (oral gavage)

(TR-571: https://ntp.niehs.nih.gov/results/summaries/chronicstudies/index.html)

In rats, no treatment-related neoplastic lesions were observed. Non-neoplastic lesions related to treatment included hepatocellular hypertrophy, centrilobular fatty change and cystic degeneration.

In contrast to the rats, there were obvious carcinogenic effects attributed to kava administration in mice, manifesting as hepatocellular tumors (adenomas and carcinomas). Histologically, hepatocellular adenomas were variably sized, nodular lesions composed of well-differentiated, neoplastic hepatocytes that typically compressed the adjacent hepatic parenchyma. Portal areas and central veins were typically absent, and mild cellular atypia was often present.

Hepatocellular carcinomas were well demarcated from the surrounding hepatic parenchyma and were composed of neoplastic hepatocytes that displayed mild-to-marked cellular and nuclear pleomorphism and mitoses. The predominant pattern displayed by most neoplasms in this study was trabecular, although focal areas had glandular or solid patterns of growth. Necrosis was occasionally quite extensive, and metastasis to the lung was frequently observed. Hepatoblastomas tended to arise within hepatocellular adenomas or carcinomas and were composed of small, basophilic fusiform cells with a high nucleus-to-cytoplasm ratio. Mitoses, large, irregularly shaped cystic areas filled with blood, and areas of necrosis were common.

Additional treatment-related pathological findings in the liver included centrilobular hypertrophy, eosinophilic focus, angiectasis and hepatocellular necrosis. Centrilobular hypertrophy was characterized by enlargement of centrilobular hepatocytes with increased amounts of eosinophilic cytoplasm and enlarged nuclei. This lesion was often variable in its presence and severity between lobes and within regions of the same lobe. Eosinophilic foci consisted of well-differentiated hepatocytes containing increased amounts of eosinophilic cytoplasm. Portal areas and central veins were often present, and minimal compression of the adjacent parenchyma occurred occasionally. Hepatocellular necrosis was characterized by focal, widely scattered, randomly distributed areas of necrosis of hepatocytes often infiltrated by small numbers of mixed inflammatory cells. Necrosis was not diagnosed when it was deemed to be secondary to neoplasia. Angiectasis was characterized by variably sized dilatations of the hepatic sinusoids, typically occurring in small clusters randomly arranged throughout the hepatic parenchyma and without a sub-anatomic orientation. The sinusoids were lined by an attenuated-to-unapparent endothelium.

3-4. Aloe vera nondecolorized whole leaf extract - Male and female rats and mice (drinking water)

(TR-577: https://ntp.niehs.nih.gov/results/summaries/chronicstudies/index.html)

A neoplastic response was observed mainly in the large intestine of rats. The main findings were well-differentiated adenomas, that created distorted, glandular structures that often compressed the adjacent mucosa. In case stromal invasion into the submucosa and/or muscularis was evident, together with anaplastic changes of the epithelial cells, a diagnosis of carcinoma was made.

Non-neoplastic lesions related to treatment were also observed mainly in the large intestine and associated mesenteric lymph nodes, and included mucosal hyperplasia that was more prevalent in the ascending and transverse colon, the same locations were neoplasms were found in higher incidence, and degeneration and hyperplasia of the mesenteric lymph nodes.

In contrast to the rats, there were no treatment-related neoplastic lesions in mice, but similarly, non-neoplastic lesions related to treatment were found mainly in the colon and included goblet cell hyperplasia that was associated with cellular infiltration of the mesenteric lymph nodes. In addition, hyaline droplets (hyaline degeneration) of the nose were found in higher incidence in male mice. The microscopic appearance of the hyaline degeneration of the respiratory epithelium was typical of that seen with the spontaneously occurring hyaline degeneration of the olfactory and respiratory epithelium in B6C3F1 mice and consisted of accumulation of homogeneous eosinophilic material within the cytoplasm of epithelial cells. Hyaline droplets are considered by pathologists to be a commonly observed non-specific change that occurs in aging mice and is considered a non-specific adaptive response to the inhalation irritants.

3-5. Ginseng – Male and female rats and mice (oral gavage)

(TR-567: https://ntp.niehs.nih.gov/results/summaries/chronicstudies/index.html).

There were no treatment-related increases in tumors in rats and mice and there was no clear evidence for other major target organ toxicity.

3-6. Milk thistle extract– Male and female rats and mice (feed)

(TR-565: https://ntp.niehs.nih.gov/results/summaries/chronicstudies/index.html).

No treatment-related increase in tumors was observed in

rats. The incidence of mammary gland fibroadenoma (single or multiple), which is a frequent finding in F344/N rats, was decreased in the animals treated with the higher doses. Mammary gland fibroadenoma consisted of both ductular and/or alveolar epithelium and fibrous connective tissue, and its texture and consistency are related to the amount of collagen present.

There was an increase in the incidence of clear cell, eosinophilic, and mixed cell foci in the liver of female rats, although in males, there was a decrease in the incidence of mixed inflammatory cell infiltration. There was also a significant decrease in the incidence of bile duct hyperplasia in the high dose males and all groups of females.

Decreased incidence of mesenteric lymph node pigmentation was observed in all exposed groups of males and females.

Similar to the findings in rats, there was also no treatment-related increase in tumors in mice. Actually, in male mice, there was a negative trend with treatment in the incidence of hepatocellular adenoma, hepatocellular carcinoma, and hepatocellular adenoma or carcinoma (combined). There was also a decreased incidence of clear and mixed cell foci and hepatocytic cytoplasmic vacuolization in the liver of all treated male groups. Although the lower incidence of hepatocellular adenoma or carcinoma in males may be due to the decreased body weights, this might represent a direct effect of the milk thistle extract exposure on tumor formation.

The incidence of lymphoid hyperplasia was lower in the high dose females. Lymphoid hyperplasia is an age-related change, occurring after involution, and may be located either in the medulla, where the lymphocytes are organized in follicle-like structures, or in the cortex, where focal accumulations of lymphocytes are associated with the presence of patchy atrophic changes.

3-7. Turmeric Oleoresin – Male and female rats and mice (feed)

(TR-427: https://ntp.niehs.nih.gov/results/summaries/chronicstudies/index.html)

No evidence for a carcinogenic reaction was observed in male rats. There was an equivocal evidence for a carcinogenic reaction in female rats based on the finding of clitoral gland adenomas. However, there was no increased incidence of clitoral gland hyperplasia and a clear dose-response was not observed. Therefore, this finding cannot be unequivocally related to the treatment.

Inflammation was observed in several locations in the gastro-intestinal tract. There was an increase in hyperplasia, ulceration, and hyperkeratosis of the forestomach in male rats, which were considered regenerative and not part of a neoplastic reaction. Low degree ulcers, inflammation and hyperplasia were seen in the cecum and colon of male and female rats. The epithelial hyperplasia was characterized by increased thickness of the surface mucosa with outgrowths or down growths of cecal epithelium, which formed glands deep within the submucosa. Although the glands extended into the submucosa, there was normal cell differentiation and cellular atypia was not present. Although these lesions can be attributed to a direct toxic effect of the treatment, there was no evidence for a neoplastic process in the cecum.

In mice, there was an increase in the incidence of hepatocellular neoplasms in both sexes. However, this increase was not statistically significant, and there was no associated increase in hepatic foci. Therefore, this finding was considered to be of only equivocal evidence of carcinogenic activity.

4. Prospects

The National Institute of Health and Environmental Sciences (NIEHS)/NTP has studied herbal medicines to identify potential toxicities in a series of GLP rodent studies. Only part of the tested herbal drugs was found to have a carcinogenic effect in the studies, including ginkgo, goldenseal, kava, Aloe vera whole leaf non-decolorized extract, while the other herbal medicines (ginseng, milk thistle, and turmeric oleoresin) had no or equivocal evidence for carcinogenic activity. It should also be noted that the International Agency for Research on Cancer has also concluded that whole leaf extract of Aloe vera, Goldenseal root powder, Ginkgo biloba extract and Kava extract are possibly carcinogenic to humans (Group 2B)[11].

The results of these studies together with the support from additional clinical trials from other NIH institutes would provide a more complete evaluation of the risk and benefits from herbal medicine use. A review of all the NIH data (https://clinicaltrials.gov/) after completion of the clinical trials may yield important new insights for herbal medicine use.

References

1) L. Kristanc and S. Kreft, European medicinal and edible plants associated with subacute and chronic toxicity part I: Plants with carcinogenic, teratogenic and endocrine-disrupting effects, *Food Chem. Toxicol.,* **92**, 150-64(2016).
2) M. Ekor, The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety, *Front. Pharmacol.,* **4**, 177(2014).
3) K. Gromek, N. Drumond and P. Simas, Pharmacovigilance of herbal medicines, *Int. J. Risk Saf. Med.,* **27**, 55-65(2015).
4) L.N. Vandenberg, T. Colborn, T.B. Hayes, J.J. Heindel, D.R. Jr. Jacobs, D.H. Lee, T. Shioda, A.M. Soto, F.S. vom Saal, W.V. Welshons, R.T. Zoeller and J.P. Myers, Hormones and endocrine-disrupting chemicals: low-dose effects and nonmonotonic dose responses, *Endocr. Rev.,* **33**, 378-455 (2012).
5) J.K. Dunnick and A. Nyska, The toxicity and pathology of selected dietary herbal medicines, *Toxicol. Pathol.* **41**, 374-86 (2013).
6) G.A. Boorman and S.L. Eustis, The pathology working group as a means for assuring pathology quality in toxicologic studies, In Managing Conduct and Data Quality of Toxicologic Studies (C. Whitmire, C.L. Davis, and D.W. Bristol, eds.) , Princeton Scientific Publishing, Princeton, NJ, 1986, pp. 271-75.
7) J.G. Hardisty and G.A. Boorman, National toxicology program pathology quality assurrance procedures. In Managing Conduct and Data Quality of Toxicologic Studies (C. Whitmire, C.L. Davis, and D.W. Bristol, eds.) , Princeton Publishing Company, Princeton, NJ, 1986, pp. 263-69.
8) A.J. Bailer and C.J. Portier, Effects of treatment-induced mortality and tumor-induced mortality on tests for carcinogenicity in small samples, *Biometrics,* **44**, 417-31 (1988).
9) W.W. Piegorsch and A.J. Bailer, Statistics for Environmental Biology and Toxicology. In (C.A. Hall, ed.) , Vol. Section 6.3.2. Chapman and Hall, London, 1997.
10) C.J. Portier and A.J. Bailer, Testing for increased carcinogenicity using a survival-adjusted quantal response test, *Fundam. Appl. Toxicol.,* **12**, 731-7(1989).
11) IARC. Some drugs and herbal products, Volume 108. 2016.

〔日本語訳(要旨)〕

米国国家毒性プログラムにおける発がん性試験でみられたダイエタリー薬用ハーブの病理

Abraham Nyska[a)] Shim-mo Hayashi[b)] Robert R. Maronpot[c)] Yuval Ramot[d)]

[a)]Consultant in Toxicologic Pathology, Timrat and Tel Aviv University
[b)]Division of Food Additives, National Institute of Health Sciences
[c)]Maronpot Consulting LLC
[d)]Hadassah Medical Center, Hebrew University of Jerusalem, The Faculty of Medicine

薬用ハーブの人気は世界中で着実に高まっており、多くの人々がこれらの製品をセルフメディケーションに利用している。これらの薬用成分は広く用いられており、利用できる製品の数は飛躍的に増大しているが、そのほとんどが潜在的な毒性や有害影響について適切に評価されてこなかった。こういった背景を基に、米国国家毒性プログラムは、アロエベラ、イチョウ葉、朝鮮人参、ゴールデンシール、カバカバ、ミルクシスル、ターメリックオレオレジンなどのよく知られている薬用ハーブの毒性と発がん性を評価するためげっ歯類を用いた2年間混餌投与試験を行った。本稿では特にこれら薬用ハーブの発がん性の可能性についてげっ歯類の病理所見をレビューし、肝細胞の発がん性(ゴールデンシール、イチョウ葉、カバ)、大腸の発がん性(アロエベラの非脱色全葉抽出物)および甲状腺の発がん性(イチョウ葉)を詳述した。これらの試験結果は、他の米国国立衛生研究所(NIH)機関による追加の臨床試験から収集された情報と共に、薬用ハーブの利用によるリスクとベネフィットに関して包括的な評価を提供するものとなるだろう。

PROFILE

Abraham Nyska

Consultant in Toxicologic Pathology,
Timrat and Tel Aviv University
DVM, Dipl. ECVP, Fellow IATP

Dr. Nyska is an Expert in Toxicologic Pathology; Visiting Full Professor of Pathology, Tel Aviv University. Have more than 40 years of experience in pre-clinical risk assessment of chemicals, drugs, medical devices and stem cells. For 18 years, he served as Expert in Toxicologic Pathology at the American National Toxicology Program (NTP) of the National Institute of Health (NIH). From 2005, Dr. Nyska is a consultant in Toxicologic Pathology. He is Associate Editor of "Toxicologic Pathology", and a co-author of more than 450 peer reviewed publications and/or chapters in books. He is a member of international expert committees for harmonization of terminologies in toxicologic pathology (IN-HAND initiative).

Shim-mo Hayashi

Division of Food Additives, National Institute of Health Sciences
Visiting Professor, Tokyo University of Agriculture and Technology
Visiting Scientist, Osaka Prefecture University
DVM, MS, PhD, DJSTP, DJCLAM, FIATP

Dr. Hayashi received his Doctorate of Veterinary Medicine in 1985 from Osaka Prefecture University College of Veterinary Medicine, an MS in veterinary pathology from Osaka Prefecture University, completed an anatomic and molecular pathology residency at Osaka City University Medical School, and a PhD degree in veterinary and toxicologic pathology from Osaka Prefecture University. He went to National Institute of Environmental Health Sciences, North Carolina in the United States as a guest pathologist from 1999 to 2000. He is a diplomate of the Japanese Society of Toxicologic Pathologists (JSTP) as well as the Japanese College of Laboratory Animal Medicine, and is a Fellow of the International Academy of Toxicologic Pathology (IATP). Dr. Hayashi is globally recognized for his scientific expertise and serves in multiple scientific advisory roles including the IATP Accreditation Committee representative for Asia/Pacific Region, the JSTP board of Directors and Chairperson of the JSTP International Committee. He is an *ad hoc* member of Global Toxicologic Pathology President's Groups. He is also an active member of the Executive Council of Global Editorial Steering Committee (GESC) of the International Harmonization of Nomenclature and Diagnostic Criteria for Lesions (INHAND). GESC oversees the overall objectives of the INHAND projects to perform a collaborative process to review, update, and harmonize existing nomenclature documents and databases. Based on his scientific and technical credentials and scientific knowledge, Dr. Hayashi serves a current official member of the Japanese delegation for CODEX Committee of Food Additives. He serves as a council of several professional societies other than JSTP including the Japanese Society of Veterinary Science, the Japanese Society of Toxicology, and the Japanese Society of Food Chemistry. In addition to several journal editorial boards, he served the Director of Foods and Food Ingredients Journal of Japan from 2017 to 2019. He received an Outstanding Contribution in Reviewing Award from "Food and Chemical Toxicology" in 2017. He has published numerous peer-reviewed journal articles and book chapters, and most recently he co-edited the JSTP Textbook entitled "Toxicologic Histopathology" in 2017 (Nishimura Company Limited, Tokyo, Japan). He has been fostering and promoting the need for global harmonization and assessment of multiple regulatory safety requirements for food additives especially food flavorings and food colorants.

Robert R. Maronpot
Maronpot Consulting LLC
DVM, MS, MPH, DACVP, DABT, FIATP

Dr. Maronpot received his Doctorate of Veterinary Medicine in 1965 from Michigan State University, an M.S. in nutritional pathology from Michigan State University in 1966, and an M.P.H. from Harvard University in 1972. He is a Diplomate of the American College of Veterinary Pathologists as well as the American Board of Toxicology and has worked over 50 years in experimental pathology with emphasis on animal models of carcinogenesis and liver histopathology. Dr. Maronpot previously served as President of the Society of Toxicologic Pathology, President of the International Academy of Toxicologic Pathologists, served on several journal editorial boards, and was Editor-in-Chief of Toxicologic Pathology from 2001 to 2004, received the Society of Toxicologic Pathology Lifetime Achievement Award in 2008. In addition to over 300 peer-reviewed publications, he has edited a comprehensive text entitled "Pathology of the Mouse" (1999) and co-edited a book entitled "Pathology of Genetically Engineered Mice" (2000).

Yuval Ramot
Associate Professor of Dermatology and Venereology, Hadassah Medical Center,
Hebrew University of Jerusalem, The Faculty of Medicine
MD, MSc

Yuval Ramot holds an MD and an MSc degree in Biochemistry from the Hebrew University of Jerusalem, Israel. Following his medical training, he has specialized in hair research in the Department of Dermatology in Lübeck University, Germany. Later, he joined the department of dermatology in Hadassah and the Center for Genetic Diseases of the Skin and Hair and focused on research of genetic skin and hair diseases and toxicology of the skin. His main clinical interest is inflammatory diseases of the skin, and he is the director of the psoriasis and hidradenitis suppurativa clinics in Hadassah. He is the recipient of the Minerva Post-Doctoral Fellowship and the Young Dermatologist International Achievement Award. He is a member of the European Hair Research Society board and the Treasurer of the Israel Society of Dermatology and Venereology. In addition, he is part of the Editorial Board of Experimental Dermatology. He has co-authored 10 chapters in books and more than 150 articles in peer-reviewed journals.