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REVIEW

Probable Roles of Nickel in Nutrient Utilisation and Animal Performance: A Review

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ABSTRACT

Nickel (Ni) is universally present in water, soil and plants and recognized as a possibly essential trace element for animals. Various possible roles of Ni in animal body have been proposed. It is an integral part of rumen urease and is required for the biosynthesis of hydrogenase enzyme. Nickel has been reported to be a bio-ligand cofactor facilitating the intestinal absorption of the Fe^{3+} in the animal. It might influence methane production since it is required by methanogenic bacteria in rumen for growth. Improvement in body weight gain, rumen urease activity, propionate production, antioxidant status, lipid and glucose metabolism has been reported in different species due to Ni supplementation but the results have been inconsistent. The maximum tolerable levels of Ni in the feeds of rodents, poultry, swine, horse, cattle and sheep have been reported to be 50, 250, 250, 50, 100 and 100 ppm, respectively. Nickel also interacts with other minerals like iron, zinc, copper and manganese. Hence, studies are required to elucidate the functionality of Ni in animal body.

Key words: Animal production, Metabolism, Nickel, Nutrient utilisation

INTRODUCTION

Trace elements may be classified as essential or non-essential. An essential trace element is an element which is required in very minute quantities for the proper growth, physiology and development of the organism. Apart from many trace minerals whose essentiality is well established, additional transition elements have been shown or postulated to be essential since 1960s. These elements have been grouped as newer trace elements. Nickel (Ni) falls into the category of newer trace elements. According to NRC (2005), Ni is considered a 'possibly essential trace element'. It is the 22nd most abundant element and 7th most abundant transitional metal with an atomic number of 28 and atomic weight of 58.71.

Nickel is present in soil, water, air and the biosphere and usually in concentrations considerably higher than which is normally present in animal fluids and tissues. Nickel can exist in oxidative forms namely -1, 0, +1, +2, +3 and +4. Nickel is poorly absorbed by the animal body. Ni is transported in blood plasma by binding to albumin and some small ligands such as amino acids (*e.g.* histidine, cystine) and with small peptides. Major route for the elimination of absorbed Ni is by urinary excretion. The Ni that is unabsorbed from the diet passes through the gut and is excreted through faeces (Von, 1997). Requirements of Ni for domestic animals are not well established, however, its deficiency is known to show specific symptoms. However, with certain exceptions, no definite functions of Ni in livestock particularly in large ruminants have been assigned. Therefore, probable roles of Ni and its potential use in animals have been dealt henceforth.

DISTRIBUTION OF NICKEL IN WATER, SOIL AND PLANTS

Nickel is a ubiquitous trace element that forms approximately 0.008% of the earth's crust and ranks 24th in a crustal abundance of all elements (Ciurli and Mangani, 2001). In biological systems, the divalent form of Ni^{2+} is predominant and forms complex with organic and inorganic compounds (Alloway, 1990). The nickel content of drinking water is typically very low *i.e.* less than 10 ìg/kg (NRC, 1980). Information on Ni content of soil and feeds is very limited. The Ni contents in soils

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ranged from 2-750 ppm and the normal range in plants was 0.02-5 ppm (Alloway, 1990). The site and mechanism of uptake of Ni by barley roots suggested that Ni^{2+} is absorbed actively across the plasma lemma (Korner *et al.,* 1986). Concentration of Ni in plants can be influenced by various factors like species of plant, stage of maturity, concentration of Ni in soil, availability of Ni from soil *etc.* When grown under similar conditions, legumes generally contain higher Ni than grasses (Underwood, 1977; Sapek and Sapek, 1980). In forages, Ni decreases as maturity advances. Nickel concentration in four different forages at young vegetative stage ranged from 1.05-2.98 ppm while the same forages at a mature flowering stage contained Ni in range of 0.35-0.64 ppm (Sapek and Sapek, 1980). The pH of soil highly influences the availability of soil Ni for plant uptake. The availability of soil Ni for plant uptake is highly dependent on soil pH. The addition of calcium carbonate increased pH of soil from 5.4 to 6.4 and reduced the Ni content of ryegrass and red clover from 1.95 to 0.92 and 1.98 to 1.10 ppm, respectively (Mitchell, 1957).

EFFECT OF NICKEL ON FEED INTAKE, GROWTH PERFORMANCE AND RUMEN FERMENTATION

Anke *et al.* (1977) showed that goats supplemented with Ni @ 0.1 ppm in the diet gained 21% slower as compared with those which were fed basal diet supplemented with Ni @ 10 ppm. Spears *et al.,* 1979) fed steers an adequate protein diet (13.1%) for the first period (42 days) and a low protein diet (7.4%) during the second period (28 days). Nickel was supplemented to the basal diet at a level of 0 or 5 ppm. Feed efficiency improved by Ni supplementation in first period but no difference in weight gain was noted. However, average daily gain tended to be higher for steers receiving supplemental Ni in second period. Linear increase in mean DMI and ADG without affecting feed efficiency was observed in heifers supplemented with 3.0 ppm of Ni as compared to heifers receiving 1.5 ppm or no supplemental Ni (Singh *et al.,* 2018). Bersenyi *et al.* (2004) observed positive effects on feed conversion efficiency and body weight gain in broiler chickens when their diet was supplemented with Ni @ 50 ppm. However, when Ni was added @ 500 mg/kg diet it reduced body weight gain (BWG) by 10% and resulted in poor feed conversion efficiency (FCE). Supplementation of Ni upto 10 ppm in Murrah buffalo calves did not affect feed intake, nutrient utilization and growth in Murrah buffalo calves (Thamizhan, 2020).

Nickel has been found to have effect on ruminal urease activity. In lambs fed basal purified diet low in Ni (60 ppb) and the basal diet supplemented with 5 ppm, it was found that ruminal urease activity was much lower in lambs fed the low Ni diet. The addition of 5 ppm supplemental Ni greatly increased rumen bacterial urease activity regardless of protein source (Starnes *et al.,* 1982). Urease has been shown to be a Ni metalloenzyme and found to contain six to eight atoms of Ni/mole of enzyme (Fishbein *et al.,* 1976). The addition of Ni at level of 5 mg/d given as $NiCl_2.6H_2O$ by continuous infusion into the rumen resulted in a significant increase in rumen urease activity in sheep which were given a high-energy and low protein diet (Milne *et al.,* 1990). Murrah buffalo calves supplemented with 10 ppm Ni (T_3) showed higher urease activity, propionate concentration and decreased butyrate concentration as compared to 0 (T_1) and 5 (T_2) ppm groups with no significant difference in acetate concentration (Thamizhan, 2020).

Nickel has been found to be a component of factor F430 (Whitman and Wolfe, 1980; Diekert *et. al.,* 1980, 1981), a compound present in enzyme methyl-CoM reductase of methanogenic bacteria. Nickel is required for growth by at least one species of methanogenic bacteria (Schonheit *et al.,* 1979). However, no effect of dietary Ni (0 or 5 ppm supplemental) on methane production was observed in finishing steers (Oscar *et al.,* 1987).

O'Dell *et al.* (1970) reported that Ni supplementation in male calves fed 0, 62.5, 250 and 1000 ppm of elemental Ni as $NiCO_3$ in diet increased the molar percent of propionic and decreased butyric acid while little effect was found on molar percent of acetic acid. Molar percent of ruminal propionic acid increased

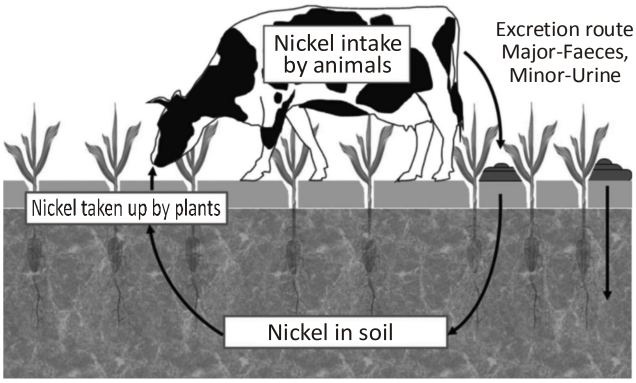

Fig. 1. Soil-plant-animal relationship of nickel

and molar percent of acetic acid decreased in steers supplemented with Ni at the level of 5 ppm. The growth of propionic acid bacteria was found to increase with addition of Ni (Vorob'eva, 1962).

METABOLISM OF NICKEL IN ANIMALS

Nickel is poorly absorbed by the body and less than 10% of intake is absorbed in the gastrointestinal tract (NAS, 1975). Yousuf *et al.* (2001) found that the rate of absorption of Ni across the intestinal mucosa was highest between two and eight hours post ingestion and that plasma Ni began to enter enterohepatic circulation after eighth hour. Because of the poor absorption of Ni, most of the ingested Ni is excreted in the faeces. After absorption, Ni is distributed to all the body organs but most of it is distributed to lungs, bones and kidneys (Samal and Mishra, 2011). The relative tissue concentrations of Ni observed in many studies were in following order: kidneys > lungs > liver > heart > testes (Ambrose *et al.,* 1976; Dieter *et al.,* 1988). O'Dell *et al.* (1971) found the highest concentration of Ni in lungs of male calves when fed non-toxic levels of Ni. Intra-peritoneal injections of ^{63}Ni were given to fifty six mice and killed at intervals after injection. Nickel was found to be cosmopolitan throughout the body but only small quantities were found in brain and muscle. The lungs had the best retention of Ni compared to other organs and a high complex-formation constant for Ni with lung protein was suggested (Wase *et al.,* 1954). Nickel is transported in plasma by binding to albumin and a small number of ligands like amino acids (*e.g.,* cystine and histidine) and little peptides.

REQUIREMENT OF NICKEL AND MAXIMUM TOLERABLE LEVELS

Semipurified diets containing 30 to 100 ppb Ni fed to lambs and goats showed deficiency symptoms in the animals (Anke *et al.,* 1980; Spears and Hatfield, 1980). Optimum Ni requirement for young ruminants was about 1 ppm. The Ni requirement for monogastric species may be between 50 and 200 ppb. A dietary Ni requirement for monogastric animals was less than 200 ppb of diet (Nielsen *et al.,* 1991).

O'Dell *et al.* (1970, 1971) reported Ni toxicity and accumulation in young male calves fed with 0, 62.5, 250 or 1000 ppm supplemental Ni as Ni carbonate and feed intake was slightly decreased and body weight gain was not affected in animals when fed with 250 ppm Ni in diets. When the calves were fed with 1000 ppm Ni, it decreased feed intake and body weight but they were not thin and appeared to be younger than the other calves. According to NRC (2005), maximum tolerable levels of Ni in the feeds of rodents, poultry, swine, horse, cattle and sheep have been reported to be 50, 250, 250, 50, 100 and 100 ppm, respectively.

BIOCHEMICAL ROLES OF NICKEL

Nickel functions either as a structural compound or as a cofactor for enzymes in the animal body. It was found in factor F_{430} (Diekert *et al.,* 1980) present in methanogenic bacteria. So for growth, Ni was required by at least one species of methanogenic bacteria (Schonheit *et al.,* 1979). Spear *et al.* (1979) showed that low protein and high energy diet with Ni supplementation fed to ruminants led to a greater response of urease enzyme activity. In this study, diet

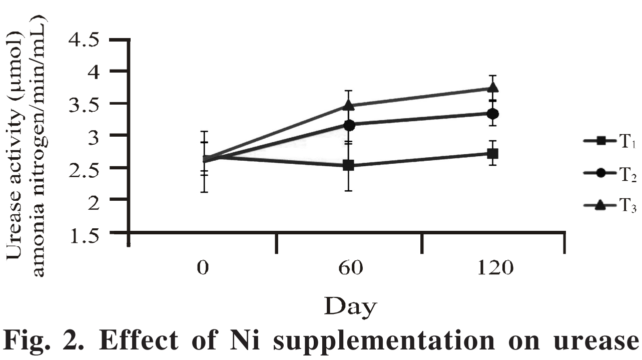

Fig. 2. Effect of Ni supplementation on urease activity in Murrah buffalo claves

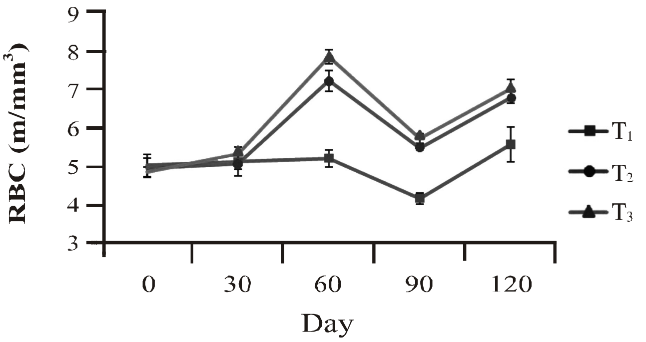

Fig. 3. Influence of Ni supplementation of RBC level in Murrah buffalo calves

containing 5 ppm Ni fed to steer and lamb showed an increase in body weight gain, urease activity and reduced serum urea concentration. Nickel with marginal or adequate protein diets containing urea increased rumen ammonia concentration and serum urea (Spear *et al.,* 1978c; Spears *et al.,* 1979; Starnes *et al.,* 1982). Thamizhan (2020) found that urease activity in rumen fluid was highest in Murrah buffalo calves supplemented with 10 ppm (T_3) Ni in comparison to 5 ppm (T_2) and 0 ppm (T_1) supplemented groups (Fig. 2).

Nickel has a bio-ligand cofactor facilitating the intestinal absorption of the Fe^{3+} in the animal. The interrelationship between iron and Ni was investigated in rats. Schnegg and Kirchgessner (1976) suggested that Ni deficient diet fed to rats showed a decrease in RBC counts, haemoglobin concentration and hematocrits values. It was due to reduced Fe absorption. Nickel absorption improved when Fe deficient diet was fed to rats thus inferring a common intestinal transportation system (Becker *et al.,* 1980). Thamizhan (2020) found that the values of RBC (Fig. 3), Hb (Fig. 4) and haematocrit (Fig. 5) were the highest in Murrah buffalo calves supplemented with 10 ppm Ni in comparison to 5 ppm and 0 ppm supplemented groups.

Nickel is an important element for the biosynthesis of carbon monoxide dehydrogenase and hydrogenase enzymes (Can *et al.,* 2014) and is also found in several genera of rumen bacteria. Ni-Fe hydrogenase enzyme was required for growth of anaerobic *Enterobacteriaceae* and this bacterium was required for vitamin B_{12} synthesis in the rumen. Cellular Ni was found to be contained in the nucleic acid (Sunderman *et al.,* 1965) and contribute to the stability of RNA, DNA or ribosome suggesting that Ni might have a function in the nucleic acid or protein metabolism. Nickel deprivation in rats given 13μg Ni / kg DM showed decreased activity of malate dehydrogenase and isocitrate dehydrogenase, however, activity of aconitase decreased indicating influence or role of Ni in TCA cycle (Fig. 6) in liver (Stangl and Kirchgessner, 1995).

Spears *et al.* (1977) suggested involvement of Ni in protein metabolism based on lower urinary N and more retention of absorbed N in lambs supplemented with 5 ppm Ni as compared to lambs receiving basal purified diet low in Ni (0.065 ppm). Stangl and Kirchgessner (1996) observed that rats deprived of Ni (13 μg Ni/kg DM) had higher serum albumin and total protein concentration where as urea level was not altered as compared to control group given Ni @ 1ppm and suggested that protein metabolism is influenced by Ni deficiency. Thamizhan (2020) found that the values of blood metabolites like plasma total protein, albumin, globulin, triglycerides, non-esterified fatty acids, creatinine and blood urea nitrogen were similar, however, plasma glucose concentration was the highest and that of total cholesterol lowest in Murrah buffalo calves supplemented with 10 ppm Ni in comparison to 5 ppm and 0 ppm supplemented groups.

Decreased triglyceride content in blood serum of hens supplemented with Ni at level of 2000 ppm was observed as compared to hens receiving no

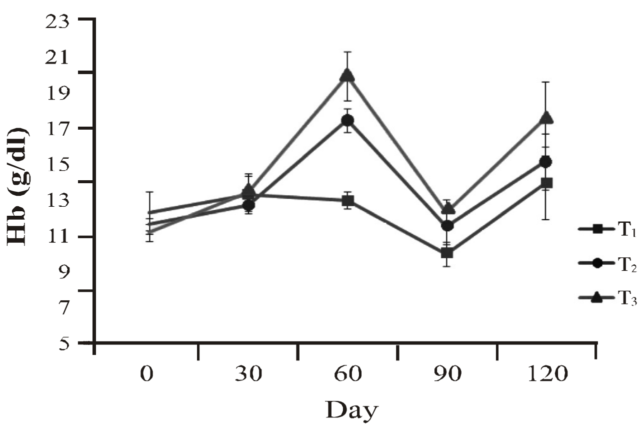

Fig. 4. Effect of Ni supplementation on Hb level in Murrah buffalo claves

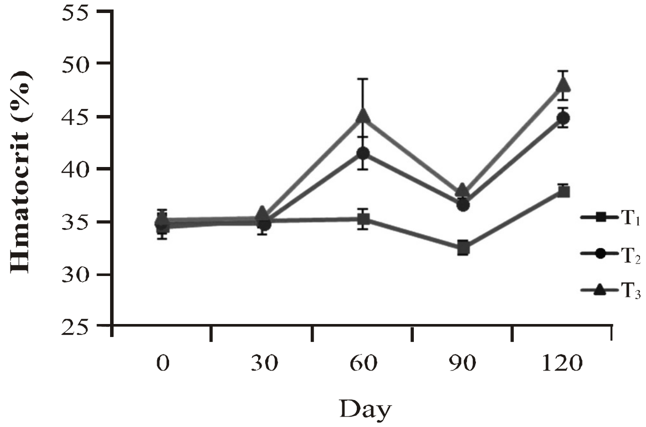

Fig. 5. Influence of Ni supplementation on haematocrit value in Murrah buffalo claves

supplemental Ni (Capcarova *et al.,* 2008). Eastin and O'Shea (1981) did not found any significant differences in plasma triglyceride and cholesterol of mallards after Ni treatment. Nickel supplementation upto 3 ppm did not affect mean plasma concentration of glucose, cholesterol and triglyceride in Hariana heifers (Singh *et al.,* 2018). No difference in cholesterol, phosphatidylcholine, phosphatidylethanolamine and phosphatidylserine was observed in liver of Ni deficient rats (Stangl and Kirchgessner, 1996). Bwititi and Ashorobi (1998) recorded increase in plasma glucose of rats in response to Ni supplementation. Spears *et al.* (1979) showed that glucose in serum was not affected by dietary Ni in ruminants.

INFLUENCE OF NICKEL SUPPLEMENTATION ON ANTIOXIDANT AND IMMUNITY STATUS

Effect of Ni supplementation at level of 0, 1.5 and 3 ppm on antioxidant and immunity status of Hariana heifers was studied by Singh *et al.* (2018). Concentrations of plasma total antioxidant status exhibited a linear decrease in groups supplemented with Ni where no effect of its supplementation was observed on catalase activity, plasma lipid peroxidase and superoxide dismutase (SOD) concentrations. Supplementing Ni up to 3 ppm of diet DM did not show any effect on plasma total Ig and IgG concentrations where as a negative relation was found to be there between plasma cortisol level and supplemented Ni levels and lowest concentration was found to be in 3.0 ppm Ni supplemented group. Thamizhan (2020) found that the values of total anti-oxidant status, activity of SOD and GPx remained similar, however, catalase activity was higher (P<0.05) in Murrah buffalo calves supplemented with 10 ppm Ni as compared to 5 and 0 ppm supplemented groups. In mice exposed to Ni, immunoglobulin IgG and IgM levels along with the proliferative responses of B cells to mitogen lipopolysaccharide were depressed (Schiffer *et al.,* 1991).

INTERACTION OF NICKEL WITH OTHER MINERAL ELEMENTS

Nickel has been found to interact or influence the metabolism of a number of other mineral elements. Spears *et al.* (1986) studied the effects of Ni supplementation in diet and protein on tissue concentrations of Ni, Fe, Zn, Cu and Mn. Levels of protein in the diet were 10.00, 12.25 and 14.50% and Ni was supplemented @ 0 or 5 ppm of diet. Nickel concentration in serum, liver, lung and kidney increased with supplemental levels of Ni. An interaction of Ni and protein was noted for kidney Ni. Supplementation of Ni increased Ni in kidney to a greater degree in calves fed protein @ 10.0% as compared to the calves fed higher levels of protein. Concentration of Fe in muscle, liver and lung while concentration of Mn in muscle decreased by supplementing Ni. No effects were

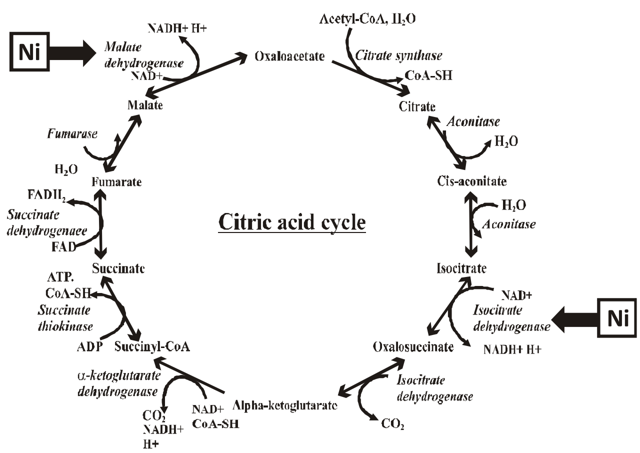

Fig. 6. Probable role of Ni in carbohydrate metabolism

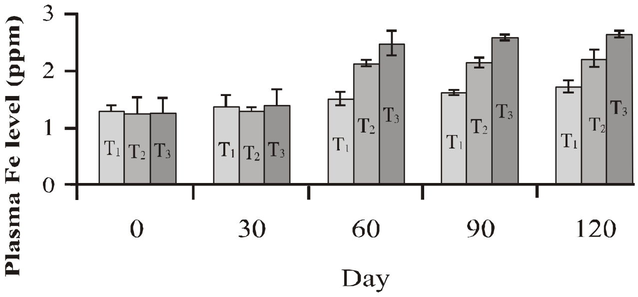

Fig. 7. Effect of Ni supplementation on plasma Fe level in Murrah buffalo claves

observed on Zn and Cu concentrations in organs.

When rats were fed Ni deficient diet containing 50 mg/kg of Fe, it decreased RBC count, hemoglobin concentration and hematocrit value (Schnegg and Kirchgessner, 1975). As the dietary iron level was increased to 100 mg/kg, minor anemia was apparent in Ni deficient rats. There was reduction in Fe absorption by 33 - 73% depending on Fe concentration in rats receiving 0.015 ppm Ni as compared with group fed @ 20 ppm Ni (Schnegg and Kirchgessner, 1976). High dietary levels of Fe have been shown to prevent Ni toxicity in chicks (Hill, 1981). The retention of Fe was found to be higher in Murrah buffalo calves supplemented with 10 and 5 ppm Ni in comparison to group given no supplemental Ni while plasma concentration of Fe was the highest ($P<0.05$) in group 10 ppm followed by 5 and 0 ppm group (Thamizhan, 2020).

The deficiency of Ni lowered the Zn concentrations in tissue in pigs (Anke *et al.,* 1974), lambs (Spears *et al.,* 1978) and goats (Anke *et al.,* 1980). Spears *et al.* (1979) found that concentration of Fe in lung increased while concentration of Zn in spleen decreased in lambs supplemented with Ni at the rate of 5 ppm as compared to lambs receiving basal diet only without Ni supplementation. When rats were fed Cu deficient diets, Ni supplementation tended to decrease tissue concentration of Cu (Spears *et al,* 1977). Copper and Ni interaction is influenced by levels of dietary Fe (Nielsen and Zimmerman, 1981). Thamizhan, (2020) found that Fe concentration in plasma was highest in Murrah buffalo calves supplemented with 10 ppm Ni in comparison to 5 ppm and 0 ppm supplemented groups (Fig. 7).

DEFICIENCY SYMPTOMS OF NICKEL IN DIFFERENT SPECIES

Nielsen *et al.* (1972) produced Ni deficiency (2-15 ng of Ni /g of diet) in chicks under near optimal growth conditions. Nickel deprivation caused changes in ultrastucture of the liver, decrease in lipid phosphorus within the liver, disorganized ER gross appearance, reduction in oxidative ability, alteration in skin pigmentation of shank due to drecrease in yellow lipochrome pigments and lower hematocrit values. Deficiency of Ni developed in chicks given <40 ppb Ni showed pigmentation changes in the shank skin, thicker legs with slightly swollen hocks, dermatitis of the shank skin and a less friable liver (Nielsen and Sauberlich, 1970). In goats fed <100 ppb Ni reduced pregnancy rates, delayed pregnancies and birth of offspring, reduced birth weights, lower weight gains during the suckling period and increased mortality was observed (Anke *et al.,* 1978).

CONCLUSIONS

There are some evidences suggesting possible role of nickel in animal body functions which can be direct such as interaction with minerals like iron, zinc, copper, lipid and glucose metabolism or indirect such as influence on the rumen microflora exerting its effect on various rumen fermentation parameters like urease activity, total volatile fatty acid production, methane production *etc.* Nickel supplementation showed positive effect on health and production of animals in some cases. However, there are no consistent results related to effects of Ni in various animal species. Studies on ruminal VFA production, digestion, enteric methane emission, immunity, antioxidant status and growth are required to be undertaken in ruminants to ascertain their requirements. This also holds true for other animal species as well.

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